Modulatory Effects of Emotional Arousal on Cueing during Sleep and Retrieval Mechanisms

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Abstract

Emotionally arousing experiences enjoy a beneficial status in our memory. This may result from both, a greater attention deployment during encoding and enhanced subsequent consolidation mechanisms. This emotional enhancement has been reported to boost over time, indicating that emotions continue to exert an influence on memory formation, in particular across sleep. It is assumed that the beneficial role of sleep on memories is based on spontaneously occurring memory reactivations, thereby promoting the stabilization and integration of those memories. While it has been suggested that the replay process during non rapid-eye movement (NREM) sleep is selective, preferentially strengthening memories of future relevance, e.g. associated with emotional arousal, the role of rapid-eye movement (REM) sleep in emotional memory processing remains a matter of debate. Moreover, direct evidence for the preferential replay of emotional memories during REM or NREM sleep is still lacking and the underlying neural mechanisms remain unclear, in particular whether they differ from replay processes of neutral memories.

The present thesis examined specifically how emotional arousal during encoding modulates subsequent sleep-dependent consolidation mechanisms. Using a newly developed emotional association task, Study 1 validated that sleep is beneficial for the consolidation of emotional word-picture associations. In Study 2 memories for emotional and neutral associations were cued during either NREM or REM sleep. Only during NREM sleep, the replay of emotional memories resulted in a behavioral cueing benefit and this was neither observable for cueing during REM sleep nor for neutral associations. On a neural level, successful cueing during NREM sleep was associated with increases in oscillatory theta and spindle power and more often followed by frontal slow waves.

Study 3 investigated whether cueing during sleep would lead to enduring changes in oscillatory activity during subsequent retrieval testing. During the recall of previously replayed associations during NREM sleep, alpha power was decreased, which was even stronger for cued remembered. Moreover, the emotionally arousing cued and remembered trials showed the strongest alpha desynchronization, nicely reflecting the cueing effects on memory performance.

Summarizing, the present thesis investigated the memory enhancing effects of cueing emotional memories during NREM and REM sleep and the underlying neural mechanisms. The results suggest that the reactivation of emotionally arousing memories during NREM sleep relies on a similar mechanism as for neutral memories. This mechanism is presumably modulated by the level of experienced arousal during encoding, further facilitating the triggering of targeted memory reactivations and thereby enhancing subsequent retrieval processes.

Zusammenfassung

Emotionale Ereignisse bleiben stärker in unserem Gedächtnis haften als alltägliche Erlebnisse. Dies könnte dadurch zustande kommen, dass sie einerseits mit einer erhöhten Aufmerksamkeit enkodiert und andererseits, dass sie anschliessend verstärkt konsolidiert werden. Es wird angenommen, dass die Gedächtniskonsolidierung im Schlaf zu letzterem beiträgt und im Schlaf insbesondere emotionale Erinnerungen gefestigt werden. Dies basiert auf spontanen Gedächtnisreaktivierungen im Hippocampus während des non rapid-eye movement (NREM) Schlafs, die zu einer Stabilisierung und Integration der Gedächtnisinhalte führen. Diese Art von Gedächtniskonsolidierung ist möglicherweise selektiv, und es werden im Schlaf insbesondere emotionale Erinnerungen gefestigt. Während NREM Schlaf in verschiedenen Konsolidierungsmodellen eine zentrale Komponente darstellt, bleibt die Rolle von rapid-eye movement (REM) Schlaf umstritten und es ist noch kein Nachweise dafür erbracht worden, dass emotionale Gedächtnisinhalte tatsächlich bevorzugt während REM oder NREM Schlaf reaktiviert werden. Ausserdem stellt sich die Frage, ob sich die zugrundeliegenden neuronalen Mechanismen zwischen emotionalen und neutralen Gedächtnisreaktivierungen unterscheiden.

Die vorliegende Dissertation umfasst drei Studien, die sich mit dem Einfluss von emotionalem Arousal beim Enkodieren auf schlafabhängige Gedächtniskonsolidierung beschäftigt haben. In der ersten Studie konnte die schlafabhängige Gedächtniskonsolidierung eines neuen emotionalen Assoziationsparadigma validiert werden. In der zweiten Studie wurden emotionale und neutrale Gedächtnisinhalte im NREM oder REM Schlaf expermentell reaktiviert. Einzig das Einspielen von emotionalen gedächtnisassoziierten Cues im NREM Schlaf führte zu einer verbesserten Gedächtniskonsolidierung, neutrale Gedächtnisinhalte konnten jedoch nicht davon profitieren. Das Einspielen im REM Schlaf hatte generell keine gedächtnisförderliche Wirkung, weder für emotionale noch neutrale Assoziationen. Während NREM Schaf war erfolgreiches Einspielen, will heissen später erinnerte Assoziationen, auf neuronaler Ebene mit verstärkter Theta und Spindel Aktivität verbunden und es folgten häufiger langsame Oszillationen.

Die dritte Studie untersuchte, ob das Einspielen im NREM Schlaf zu einer veränderten oszillatorischen Aktivität während dem darauf folgenden Erinnerungstest führt. Während dem Abruf von Assoziationen, die zuvor im NREM Schlaf eingespielt worden waren, zeigte sich eine verringerte Aktivität im Alpha Bereich, was besonders ausgeprägt war für erfolgreich eingespielte emotionale Assoziationen. Das Ergebnismuster der oszillatorischen Analyse spiegelt, wie schon in der zweiten Studie, den Gedächtnisförderlichen Effekt von Cueing wider.

Die vorliegende Arbeit untersuchte die Gedächtnisförderliche Wirkung des Cueings von emotionalen Assoziationen im NREM und REM Schlaf. Die Ergebnisse legen nahe, dass diesselben neuronalen Mechanismen für die Konsolidierung von emotionalen und neutralen Gedächtnisinhalten während NREM Schlafs zuständig sind, diese jedoch durch das Ausmass der erlebten Arouals während des Enkodierens moduliert werden. Dies führt möglicherweise zu einer verstärkten Reaktivierung während dem Schlaf und unterstützt dadurch die Abrufmechanismen am darauffolgenden Tag.

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I. Introduction

1.1 Background

Memories lie at the very core of our conscious experiences. They are shaped by our environment but influence in turn also critically how we perceive and relate to our environment. Aside from physical differences, the fact that there are not two human beings sharing the exact same experience or experience the same event as congruent, is essentially defining our personality. Given this crucial role in cognition and individuality, a complete understanding of how memories are formed on a psychological, cognitive and neurobiological level is a pivotal goal of a multidisciplinary research approach. In the last decades of memory research, sleep has become increasingly important when it comes to processes that are beneficial for the strengthening of memories. Over a century ago, Ebbinghaus provided first evidence that sleep benefits memory by reducing the amount of forgetting (Ebbinghaus, 1992). Since then a large number of studies corroborated the positive effect of sleep on memory and great advances have been made in the mechanistic understanding, suggesting that the sleeping brain processes memories actively (Ellenbogen, Payne, & Stickgold, 2006). In addition to sleep, emotional arousal has also been critically implicated in enhancing memories. Although they might not be an accurate preservation, the memory of the first school day or – in more unpleasant examples – of a live-threatening situation or the witnessing of a violent car accident can revive in more details and more vivid than everyday experiences. It is not without reason that William James wrote that some events are "so exiting emotionally as almost to leave a scar upon the cerebral tissues" (James, 1885).

The following sections target in a first step the field of 'sleep and memory' and oscillatory mechanisms of memory formation during wake and sleep. Subsequent sections will address the effects of emotion on memory and in particular the question to what extent emotional memories enjoy a preferential or even selective sleep benefit. In the last section, empirical findings from fundamental and clinical research are linked and the differential roles of rapid-eye movement (REM) and non-REM (NREM) sleep are discussed.

1.2 Sleep and Memory

From a cognitive psychologist's perspective, the variety of fundamental cognitive and neurobiological processes for memory acquisition can be roughly divided into three intermediate stages: encoding, consolidation and retrieval (Gabrieli, 1998). During encoding, information is processed and transformed into a new, initially labile memory representation. Already at this early stage, memories formation can be enhanced by a number of factors, e.g. the allocation of attentional resources to the stimulus or elaborating on its meaning. Once encoded, the process of consolidation determines the strengthening and stabilization of memories. Memory consolidation can be improved decisively by effective initial encoding and undisturbed consolidation mechanisms. After successful encoding and consolidation of memories, the event or stimulus has to be retrieved. Retrieval characterizes the accessing of the previously learned material.

While encoding and retrieval are optimally performed in the state of wakefulness, it has been consistently shown that sleep after learning is highly beneficial for consolidation mechanisms, resulting in an improved retrieval performance (Rasch & Born, 2013). The putative processes underlying this beneficial effect have been described and conceptualized within the active system consolidation hypothesis (Diekelmann & Born, 2010). This model for memory consolidation during sleep attempts to integrate a variety of findings and refers to the standard two-stage model of memory (Marr, 1971; McClelland, McNaughton, & O'Reilly, 1995), a general concept that distinguishes between a fast-learning and a slow-learning store, which are represented by the hippocampus and the neocortex, respectively. Initial encoding critically relies on a fast-learning system, thus on the hippocampus. However, during system consolidation, memory representations are redistributed into a slow-learning memory system in cortical brain areas where they are integrated into larger neocortical networks and lose their dependency on hippocampal structures during retrieval (e.g. Frankland & Bontempi, 2005). A central assumption of the active system consolidation is that this gradual redistribution process is driven by spontaneous and repeated reactivations of previously encoded memories during sleep such that synaptic connections within the neocortex are

strengthened and form a more persistent memory representations (Rasch & Born, 2013). There is now compelling evidence from rodents as well as humans that patterns of neuronal firing particular in the hippocampus that were present during encoding are replayed during subsequent sleep in the same sequential order (Wilson & McNaughton, 1994; O'Neill, Pleydell-Bouverie, Dupret, & Csicsvari, 2010; Pavlides & Winson, 1989; Peigneux et al., 2004; Peyrache, Khamassi, Benchenane, Wiener, & Battaglia, 2009). However, reactivations occur not only in the hippocampus but also in other brain regions involved in for memory consolidation (Ji & Wilson, 2007; Pennartz et al., 2004; Peyrache et al., 2009), indicating that memory representations become gradually redistributed.

Recent work has now suggested that presenting learning-associated cues during sleep can externally trigger the otherwise spontaneous replay of memory, a technique that has become known as targeted memory reactivation (TMR; see (Oudiette & Paller, 2013) for a review). In a seminal study by Rasch and colleagues (Rasch, Büchel, Gais, & Born, 2007), participants learned an object-locations task in the evening while an odor of rose was administered. Recall performance was more accurate if the participants were re-exposed to the associated odor during subsequent slow wave sleep (SWS) as compared to when no odor was presented, suggesting that the olfactory cueing had stimulated the reactivation of individual memory representations. This interpretation has received support from a number of subsequent TMR studies extending the body of evidence by showing that not only contextual cues such as odors but also cues that were part of the learning material can improve memory consolidation (e.g. (Rudoy, Voss, Westerberg, & Paller, 2009; Schreiner, Lehmann, & Rasch, 2015; Schreiner & Rasch, 2014). Moreover, it has been reported that replay of prior learned melodies is beneficial for perceptual skill (Antony, Gobel, O'Hare, Reber, & Paller, 2012; Schönauer, Geisler, & Gais, 2014) or that explicit knowledge of a motor-task can be promoted (Cousins, El-Deredy, Parkes, Hennies, & Lewis, 2014). Recent findings from a rodent study provided evidence that presenting memory related cues during sleep can effectively manipulate replay (Bendor & Wilson, 2012).

Underpinning the assumed sleep specificity of cueing, reactivating memories during wakefulness has been found to have either no effect (Hauner, Howard, Zelano, & Gottfried, 2013; Rasch et al., 2007; Schönauer et al., 2014) or even adverse consequences on recall performance (Diekelmann, Büchel, Born, & Rasch, 2011). Using verbal cues, Schreiner and Rasch (Schreiner & Rasch, 2014) demonstrated that during wakefulness, the lack of beneficial memory effects of cueing is independent of the attentional resources available. Both, cueing during active listening or during an undemanding working memory task did not improve later recall.

1.3 Oscillatory correlates of memory during wakefulness

Extensive evidence has accumulated that neural oscillatory synchrony is essential for memory formation (Düzel, Penny, & Burgess, 2010; Fell & Axmacher, 2011). Particularly high synchronous activity in the theta (4-7 Hz) and gamma (30-80 Hz) range has been consistently shown to benefit encoding and formation of declarative memory during wakefulness, and it is widely assumed that theta and gamma oscillations are functionally related in binding of information involving the hippocampal system (Rey, Fried, & Quian Quiroga, 2014; Rutishauser, Ross, Mamelak, & Schuman, 2010; Staudigl & Hanslmayr, 2013). In particular, increases in oscillatory theta power during successful encoding was predictive for later remembering of the newly learned information (Addante & Watrous, 2011; Klimesch, 1999; Lega, Kahana, Jaggi, Baltuch, & Zaghloul, 2011), possibly representing the strength of a memory trace (Klimesch, Doppelmayr, & Hanslmayr, 2006). Similarly, it was found that gamma power was higher during successful encoding (Jutras, Fries, & Buffalo, 2009; Sederberg et al., 2007). Changes in both frequency ranges have been shown to occur in the hippocampus and more recently it was suggested that they communicate with each other across brain regions, a process called cross-frequency coupling (Friese et al., 2013; Lisman & Jensen, 2013). Adversely, memory seems also to benefit from low synchrony in the alpha range (8 - 12 Hz) during encoding (Michelmann, Bowman, & Hanslmayr, 2016; Schneidman et al., 2011; Waldhauser,

Johansson, & Hanslmayr, 2012). It is assumed that the opposing oscillatory behaviors play distinct roles in the mechanisms of memory formation: synchronization in theta and gamma activity mediates binding (Staudigl & Hanslmayr, 2013), and the neocortex showing low-frequency desynchronization has been related to the building of a semantic representation (Hanslmayr, Staudigl, & Fellner, 2012; Waldhauser et al., 2012). This pattern of synchrony was similarly reported during retrieval testing, with increases in theta (Klimesch et al., 2001) and decreases in alpha power (Hanslmayr, Staresina, & Bowman, 2016) associated with better memory retrieval.

These oscillatory mechanisms of memory formation have mainly been observed during wakefulness. However, oscillatory synchrony also plays a critical role for memory consolidation during off-line periods like sleep. As stated by the active system consolidation hypothesis, slow-oscillations (< 1 Hz) characterizing slow-wave sleep (SWS) function as a pace maker and synchronize sleep-specific spindle activity (11 – 16 Hz) with hippocampal sharp wave ripple activity to optimize the gradual redistribution of memory traces to neocortical long-term stores. It is suggested that the depolarizing up states of the slow oscillation drive repeated reactivations of memory representations in the hippocampus together with sharp wave ripples. Sharp waves are fast depolarizing bursts that become superimposed by ripple activity (100-300 Hz), representing the most prominent activity pattern in the hippocampus during Non-REM sleep (Kudrimoti, Barnes, & McNaughton, 1999). The spindle-ripple events are thought to represent the neural basis of information transfer, by priming and maintaining long term potentiation in cortical circuits by provoking Ca^{2+} influx for successive plasticity associated processes (Contreras, Destexhe, & Steriade, 1997). Thalamic and hippocampal inputs to the cortex are inhibited during sleep spindles (Peyrache, Battaglia, & Destexhe, 2011), suggesting that sleep spindles might be involved in supporting local plasticity of previously reactivated memories rather than reactivation and redistribution of memories itself (Genzel, Kroes, Dresler, & Battaglia, 2013). Further corroborating the view that the interplay of oscillatory mechanisms is crucial for successful memory consolidation during sleep, experimentally enhancing only one component, e.g. slow wave activity, failed to increase consolidation processes during sleep (Feld et al., 2013), while the concurrent enhancement of slow wave and sleep spindle activity by

pharmaceutical, electric or auditory stimulation has proven to be effective (Marshall, Helgadóttir, Mölle, & Born, 2006; Ngo et al., 2015; Ngo, Martinetz, Born, & Mölle, 2013).

Taken together, the previous sections have provide convincing evidence for a functional significance of the replay of memories during sleep and how cueing might affect consolidation and recall mechanisms. However, the consistent use of neutral stimuli raises the critical question how an emotional tone of the learning material affects TMR. It has been suggested that emotional events attain a privileged status in memory (LaBar & Cabeza, 2006), not only during encoding but also during consolidation processes. The following section will describe what differentiates emotional from neutral memory formation and how this process might be affected by sleep.

1.4 Emotion and Memory

When reviewing the effect of emotion on memories, Elizabeth Kensinger (Kensinger, 2009) refers to "flashbulb memories", a concept from the 1970ies (Brown & Kulik, 1977) describing that the occurrence of highly surprising events activates a special memory system, resulting in a more detailed preservation of the situation. Kensinger relates this phenomenon to the durability of emotional memories, where the retention is also reported to be more vivid and accurate as compared to unexciting events. Autobiographical memories for severe injuries (Peterson & Whalen, 2001), terrorist attacks (Budson et al., 2007), the outbreak of a war (Bohn & Berntsen, 2007; Tekcan, 2001) or natural disasters (Bahrick, Parker, Fivush, & Levitt, 1998) appear to be more persistent and to include more contextual information of the experience. In observational studies, it is difficult to check the reports from autobiographical memories for accuracy, however, in the last decade, growing evidence from experimental studies confirmed these findings by demonstrating that emotionally arousing stimuli are preferentially memorized as compared to neutral ones (LaBar & Cabeza, 2006; McGaugh, 2004). It has been shown that the emotional tone of a stimulus is particularly memory enhancing when it has an arousing component (Anderson, Yamaguchi, Grabski, & Lacka, 2006;

Buchanan, Etzel, Adolphs, & Tranel, 2006), suggesting that the emotional response at encoding might be critical for the fate of a memory.

During encoding, the ease of perceiving a stimulus is influenced by various factors but attending the stimulus is pivotal. Several studies have shown that emotion can critically increase the depth of processing during encoding (Fox, Russo, Bowles, & Dutton, 2001; Ohman et al., 2001) and perceiving a visual stimulus as emotionally arousing increases the neural response in the amygdala, which subsequently promotes the higher-level processing (e.g. in the visual cortex: (Amaral, Behniea, & Kelly, 2003)). The amygdala receives input about the emotional significance of a stimulus very rapidly and fires irrespective of awareness and attentional focus (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003; Vuilleumier, Armony, Driver, & Dolan, 2001; Whalen et al., 1998), such that emotional stimuli are processed preferentially. It is assumed that subsequent perception is thereby enhanced, resulting in a stronger hippocampal encoding of emotional stimuli (Davis & Whalen, 2001). However, as described above, the fate of memories is not merely determined by their encoding in an "all-or-nothing" fashion. In order that they may become part of the long-term memory, the newly encoded memories have to be consolidated and it is assumed that the initial amygdala response continues to modulate the memory formation after encoding (McGaugh, 2004). In this line, several studies have shown that activity in the amygdala at encoding is predicting later memory performance for emotional stimuli (Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Hamann, Ely, Grafton, & Kilts, 1999).

It is assumed that this disparity between emotionally high and low arousing memories is due to the co-existence of multiple memory systems that become however highly interacting when the perceived stimulus is emotional. When examining the influence of emotion on memory, researcher focus primarily on two memory systems that are both located in the medial temporal lobe. One is linked to the amygdala and plays a particularly important role in the acquisition of fear conditioning, when a person learns to predict an aversive event from an initially neutral stimulus. The other memory system encompasses the hippocampal formation and is important for the acquisition of declarative memory and recalling information at will. Clinical studies on neurological patients with

focal lesions to either the amygdala or the hippocampus have demonstrated a double dissociation between the two memory systems: Individuals with bilateral damage on the amygdala could predict that a symbol (e.g. a green circle) was associated with an electric shock but the occurrence of the symbol was not followed by a conditioned autonomic response (i.e. skin conductance response) as it would be the case in healthy participants. When the lesion was located bilaterally in the hippocampus, the opposite was the case, with no recollection at will of the shock but an arousal response when the green circle appeared (Bechara et al., 1995). Taken together, it appears that the two memory systems can function independently but in healthy individuals, the arousal system critically modulates the processing, enabling us to form lasting memories of emotional experiences.

1.5 Sleep and Emotional Memory

The observation that emotional memory enhancement increases over time (Anderson et al., 2006; Tali Sharot & Yonelinas, 2008), suggests a continuing influence of emotional arousal on ongoing consolidation processes. In particular when the retention period contains a night of sleep, emotional aspects of memories are selectively enhanced (e.g. (Payne, Chambers, & Kensinger, 2012; Sharot & Phelps, 2004)). Recent experimental approaches, using TMR, have reported evidence that cueing of emotional picture-locations during NREM sleep improved recall performance (Cairney, Durrant, Hulleman, & Lewis, 2014) and subjects who underwent a fear conditioning task in the presence of an odor showed weaker physiological response to the conditioned stimulus when they were re-exposed to the odorant contextual cue during subsequent slow-wave sleep (Hauner et al., 2013). Surprisingly and contrary to the latter finding, a rodent study reported increased freezing when the conditioned stimulus was delivered during SWS (Rolls et al., 2013). Thus, whether the attenuation, erasure or even reinforcement of emotional memories relies on mechanisms during sleep, remains unknown. Moreover, it is an ongoing debate, if a particular sleep stage, NREM or REM sleep, is beneficial for emotional memory consolidation. Traditionally, REM sleep has been

considered to consolidate specifically memories for emotional events but reviewing the literature about REM sleep and memory consolidation reveals a highly inconsistent picture (Rasch & Born, 2013). A recent model proposed that sleep might strengthen the content of emotional memories and - in particular REM sleep - reduces its associated affective tone (Walker & van der Helm, 2009). Hence, sleep would eventually contribute to habituation processes and reduce aversive reactions to arousing stimuli, contributing to emotional regulatory processes. Evidence for a role of sleep in recalibrating the emotional response after intense experiences is however inconsistent, as studies have reported depotentiating (Cunningham et al., 2014; Pace-Schott et al., 2011), but also a protective (Baran, Pace-Schott, Ericson, & Spencer, 2012; Groch et al., 2011), or even potentiating effects (Lara-Carrasco, Nielsen, Solomonova, Levrier, & Popova, 2009; Ullrich Wagner, Fischer, & Born, 2002) of sleep on emotional reactivity to arousing stimuli.

It has been proposed that REM sleep represents a neurobiological brain-state particularly beneficial to emotional memory processing (Cahill & McGaugh, 1998; Hu, Stylos-Allan, & Walker, 2006; Nishida, Pearsall, Buckner, & Walker, 2009; Wagner, Gais, & Born, 2001; Walker, 2009b; Walker & van der Helm, 2009) with theta oscillations coordinating the interaction between brain regions that were initially involved in encoding of emotional experiences (Goldstein & Walker, 2014). Thus, theta activity during REM is believed to preferentially govern the long-term consolidation of emotional experiences (Goldstein & Walker, 2014) and promote their integration intro pre-existing autobiographical memory networks (Cahill, 2000; Jones & Wilson, 2005). Moreover, the elevated activity level in limbic regions including the striatum, amygdala and hippocampus during REM sleep (Maquet, 1995; Maquet & Franck, 1997), may lead to a preferential reactivation of emotionally salient memories (Sterpenich et al., 2009).

Although clinical studies report reliably a memory bias for negative stimuli in depressed patients, remembering significantly more sad vs. happy experiences, psychiatric (Ingram, Miranda, & Segal, 1998; Surguladze et al., 2005), research has only recently started to investigate sleep-related memory consolidation in clinical populations. One of the most consistent finding is that REM sleep is altered in depression: reduced REM latency, increased REM sleep duration and density (Pillai,

Kalmbach, & Ciesla, 2011; Riemann, 2007). These findings further provide indirect evidence for the importance of sleep in emotional processing and fuel the idea of a critical role of REM in emotional memory consolidation.

1.6 Aims

Nowadays, it is widely established that sleep benefits memory and a large body of evidence suggests that presenting memory cues during sleep can promote consolidation mechanisms. While there is also a high degree of consensus in the research community, that emotions and future relevance modulate encoding mechanisms and result in a privilege in sleep-dependent consolidation, the question about the respective roles of sleep stages remains a matter of dispute. When it comes to REM sleep, the empirical evidence from experiments is inconsistent, but the marked increase in REM sleep in affective disorders remains striking. Besides observational studies, the reports from clinical population are however scarce and the assumed relationship between a negative memory bias and disturbed REM sleep needs further empirical approaches. During NREM sleep, in particular rewarded memories seem to be preferentially replayed, direct evidence for the preferential replay of emotional memories during sleep in humans is however still lacking.

The major aim of his thesis, was to test systematically the effect of inducing emotional memory reactivations during REM and NREM sleep as well as wakefulness and to describe the neural activity associated with successful memory cueings. We used a newly developed emotional association learning task that allowed us to assess the recall from two different memory systems (see section *Emotion and Memory*): declarative memory, i.e. memory at will for the association between a word and a specific picture and the mere expectancy of an arousing or non-arousing picture. The latter is traditionally used after fear conditioning as a verbal measure of the extent to which the unconditioned stimulus upon presentation of the conditioned stimulus is expected. The novelty of the task and its application as a dependent measure of sleep-dependent memory consolidation required empirical evidence that memory for emotional word-picture associations benefits actually from sleep and thus can potentially be improved by cueing during sleep.

Using subsequently the words of the learning material as memory cues during either NREM or REM sleep, we investigated the cueing effects on memory in the two groups separately. Moreover, we aimed at investigating the neural mechanisms during successful cueing, in particular whether the

emotional arousal during encoding merely modulates memory replay processes or results in fundamentally different consolidation mechanism for emotional and neutral associations.

Finally, as oscillatory changes in the theta and alpha band during successful encoding and retrieval are assumed to represent the strength of a memory trace, we aimed at describing the cueing effects on oscillatory changes in these frequency ranges and how they might be modulated by emotionality.

II. Sleep equally benefits both emotional and neutral associative memories

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Abstract

Emotions modulate memory. It has been suggested that sleep contributes to the improved memory for emotional events by preferentially consolidating emotional memories, presumably due to a selective off-line reactivation of information relevant for future behavior. We aimed at validating sleep-dependent memory consolidation in a new associative emotional memory paradigm suitable for inducing memory reactivations during sleep. We hypothesized that sleep preferentially benefits consolidation of emotional associations independently of their negative vs. positive emotional valence.

Seventy-two healthy young participants performed on an associative emotional memory task either in the evening or in the morning. During the task, they were asked to associate neutral spoken words to neutral, negative or positive pictures. Cued recall was tested after a 12-hr retention interval filled with either nighttime sleep or daytime wakefulness.

Generally, emotional associations were better remembered than neutral ones. However, we were not able to replicate a selective benefit of sleep on emotional memory. Sleep robustly improved cued recall performance of all pictures types as compared to wakefulness, without any modulating influence of emotional arousal or valence.

We conclude that consolidation of explicitly learned associations benefits from sleep independent of emotional arousal or valence. Selective emotional memory consolidation during sleep might be restricted to non-associative item memory or incidentally learned emotional associations.

Introduction

Emotional events are highly relevant for adaptive future behavior and therefore better remembered than neutral ones (LaBar & Cabeza, 2006). According to the widely accepted memory modulation hypothesis (McGaugh, 2004), consolidation of memories after encoding is strongly influenced by noradrenergic activation of the amygdala, which increases plastic processes in memory-related brain regions including the hippocampus. In support of this notion, numerous studies have demonstrated that emotions evoked by the learning material critically modulate memory consolidation (see (Kensinger, 2009), for a review). Furthermore, the memory advantage of emotional over neutral memories has been reported to increase with longer retention intervals between encoding and retrieval (e.g. (Sharot, Verfaelli, & Yonelinas, 2007; Sharot & Yonelinas, 2008), suggesting a continuing influence of emotions on ongoing consolidation processes. While most studies have examined the influence of negative emotional memories (see (Kensinger, 2009), for a review), some studies report similar or even increased memory benefits for stimuli associated with positive emotions (Ackermann, Hartmann, Papassotiropoulos, de Quervain, & Rasch, 2015; Martínez-Galindo & Cansino, 2015).

In addition to emotions, sleep has also been critically implicated in the consolidation of memories. Sleep benefits memory consolidation, presumably due to a spontaneous reactivation of newly encoded memories during subsequent Non-rapid-eye movement (NREM) sleep (see (Rasch & Born, 2013), for a review). According to the active system consolidation hypothesis (Diekelmann & Born, 2010), hippocampal memory reactivations during NREM sleep support the strengthening and integration of memories into cortical long-term stores. Furthermore, several authors have suggested that this consolidation process during sleep is selective, thereby specifically strengthening those memories that are relevant for our future behavior (Diekelmann, Wilhelm, & Born, 2009; Walker & Stickgold, 2010). Supporting this concept, reward memories are preferentially reactivated during NREM sleep in rodents

(Lansink et al., 2008; Lansink, Goltstein, Lankelma, McNaughton, & Pennartz, 2009), and sleep selectively strengthens memories associated with reward or future relevance in humans (Fischer & Born, 2009; Oudiette, Antony, Creery, & Paller, 2013; Wilhelm et al., 2011). Also for emotional memories, several studies have reported a selective effect of sleep (see (Payne & Kensinger, 2010), for a review). For example, sleep or naps preferentially consolidate memories for negative pictures or stories as compared to neutral stimuli (e.g., (Groch et al., 2011; Holland & Lewis, 2007; Hu, Stylos-Allan, & Walker, 2006; Kaestner, Wixted, & Mednick, 2013; Nishida, Pearsall, Buckner, & Walker, 2009; Payne et al., 2015; Wagner, Gais, & Born, 2001) and this effect is detectable even after several years (Ullrich Wagner, Hallschmid, Rasch, & Born, 2006). In addition, sleep also selectively improves memory for neutral stimuli incidentally associated with a negative emotional context (Payne, Stickgold, Swanberg, & Kensinger, 2008), while only one study so far provided evidence for a selective effect of sleep for positive emotions (i.e., humorous cartoons, (Chambers & Payne, 2014)).

Here we aimed at validating sleep-dependent memory consolidation in a new emotional associative memory paradigm, which is potentially capable of reactivating emotional vs. neutral memories during sleep by verbal cueing in future studies. In addition, we directly compared the selective benefit of sleep on memory for positive vs. negative emotional pictures. In the associative emotional memory paradigm, participants are instructed to learn associations between neutral, spoken words and pictures presented visually on the screen. In the negative picture group, negative and neutral pictures are used, whereas participants in the positive picture group view positive and neutral pictures. We hypothesized that sleep (as compared to wakefulness) preferentially benefits consolidation of associations between words and emotional vs. neutral pictures, independently of their emotional valence. Furthermore, we tested the effect of sleep on changes on subjective arousal ratings for the initially neutral words.

Materials and Methods

Subjects

A total of 76 healthy, right-handed subjects (16 men, age 22.1 ± 0.7 years, mean ± standard error of the mean, SEM) participated in this study. Four participants had to be excluded from the final data analysis as they reached only very low memory performance levels (less than 15 correctly recalled associations out of 100 word-picture pairs immediately after learning), resulting in a final sample of 72 (14 men, mean age 22.0 ± 0.3 years, for details see **Table 1**). Subjects were advised not to sleep or to drink coffee during the day of testing as well as to refrain from drinking alcohol before going to sleep. Using a self-evaluation questionnaire, participants reported that they were not taking any medication at the time of the experiment nor had a history of any neurological or psychiatric disorder. All subjects reported a normal sleep-wake cycle and were not or pursuing shift work for at least 8 weeks before the experiments.

Table 1: Demographic data

	N	**Age**	**m/f**
Negative Pictures Group			
Sleep	*20*	22.5 ± 0.5	15/5
Wake	*16*	21.8 ± 0.5	11/5
Positive Pictures Group			
Sleep	*19*	22.0 ± 0.9	17/2
Wake	*17*	21.6 ± 0.3	15/2

Demographic data of the experimental groups.

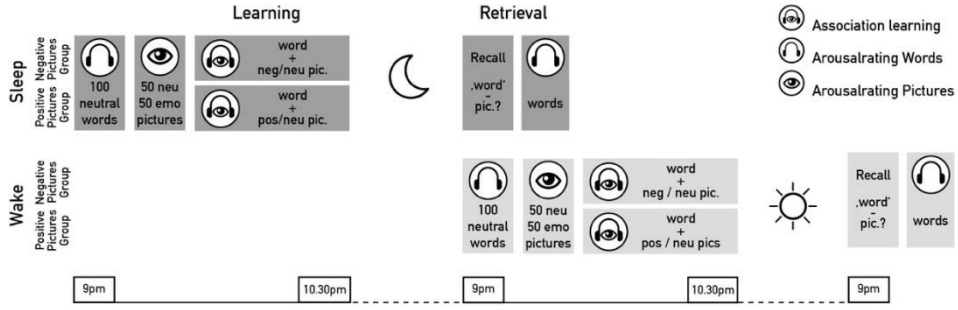
The study was approved by the ethics committee of the Department of Psychology, University of Zurich, and all subjects gave written informed consent prior to participating. After completing the whole experiment, participants received a compensation of 36 Swiss francs (CHF). We performed a power analysis to determine the sample size controlling for an error

probability of 0.05 and false negative rate of 0.1 (power of 0.9). In order to detect an emotion effect on memory consolidation over sleep of eta² = 0.1, as observed in Payne et al. (2008), a sample size of n = 44 is required.

Experimental design and General Procedure

Participants were randomly assigned to a 'sleep group' or a 'wake group'. The 'sleep group' underwent the learning phase in the evening (9 p.m.) and recall performance was testes 12 hours later in the morning. Vice versa, the 'wake group' learnt in the morning (9 a.m.) and the retrieval phase followed 12 hours later in the evening. The groups were further divided in a 'negative pictures group' and a 'positive pictures group': The 'negative pictures' sleep and wake groups learned associations between neutral words and negative as well as neutral pictures. The 'positive pictures' sleep and wake groups learnt associations between neutral words and positive as well as neutral pictures (see **Figure 1**, for a summary of the procedure; for details on the demographic parameters of the four experimental groups see **Table 1**).

Figure 1: *Experimental procedure*



During learning, participants associated 100 neutral words with 50 emotionally high arousing (emotional, 'emo') and 50 low arousing pictures (neutral, 'neu'), respectively. Participants in the 'negative pictures group' associated words with negative ('neg') and neutral pictures, whereas participants in the 'positive pictures group' associated positive ('pos') and neutral pictures. Encoding success was tested immediately afterwards using a cued recall procedure, in which participants heard the word and had to provide a brief written description of the picture. Retrieval performance was assessed after a 12 hr-retention interval of filled with either sleep or wakefulness using the same cued recall procedure. The arousal of words and pictures was rated before the learning phase and for words again after the final retrieval phase.

The first session started with subjective ratings of emotional arousal for single words and pictures separately (15-20 min). Afterwards, participants performed on the associative emotional memory task and encoded the word-picture pairs (30-35 min). After a delay of approximately 15 min during which participants filled out questionnaires, immediate memory retrieval was tested (baseline). Delayed retrieval was then tested after a retention interval of 12 hours either during day or night, respectively. Finally, participants rated again the arousal of all words without picture presentation.

The associative emotional memory task

The associative emotional memory task consisted of 100 words and pictures, which were grouped into association pairs. The words were two syllable substantives selected from the Berlin Affective Word List (BAWL-R, 2009), a German database providing normative ratings for emotional valence and arousal. The selection criterion was neutral rating with a very small standard deviation (mean rating 0 ± 0.2 SD on a -3 to +3 scale). In order to provide an auditory presentation, words were read by an actress and recorded in-house. The set of visual stimuli consisted of 150 pictures taken from the Nencki Affective Picture System (NAPS, (Marchewka, Zurawski, Jednoróg, & Grabowska, 2014)). 50 of these pictures are generally rated as neutral and low arousing. The remaining 100 pictures elicit a high level of emotional arousal, of which 50 pictures are perceived as positive and 50 as negative in emotional valence. The learning material for a single subject consisted therefore of 100 neutral words of which 50 words were associated with high arousing pictures and the other half was associated with low arousing pictures. The associations between words and pictures were balanced across participants. The emotional valence of the high arousing pictures was consistent for every participant and was either negative or positive. Participants of the study rated emotional pictures as more arousing than neutral pictures (4.52 ± 0.13 vs. 2.46 ± 0.10, t_{71} = 13.60, $P < 0.001$). In addition, negative pictures were perceived as significantly more arousing than the positive pictures (5.01 ± 0.14 vs. 4.03 ± 0.2; t_{71} = 16.22, $P < 0.001$).

Arousal ratings

Prior to the associative emotional memory task, participants rated words and pictures separately on a 7-point Likert-scale with respect to the level of arousal, ranging from 'not at all arousing' to 'highly arousing'. Following a fixating cross displayed for 1000 ms in the center of the screen, the word was presented auditory via head phones. Subsequently, the rating scale was displayed and subjects were instructed to use the keyboard to indicate the arousal elicited by the stimulus. The rating of the picture followed the same procedure during which pictures were presented visually on the screen for 1500 ms.

The learning phase

During the associative emotional learning paradigm, participants were instructed to memorize the word-picture pairs. They had to complete a total of three rounds: During the first round, the words were presented auditory after a fixation cross (1000 ms), followed by visual presentation of the picture on the computer screen. 1000 ms after picture onset, the word was played again. The picture was presented for 2500 ms followed by an inter-stimulus interval (ISI) with a random duration (1000-2000 ms). No response was required during the first learning round. During the subsequent two rounds, the first word presentation was followed by 7-point Likert-scale on which participants had to indicate whether they expected a low or high arousing picture. Subjects were instructed to press'7' (or '1'), if they expected a high (or low, respectively) arousing picture after the word with highest certainty. The button '4' indicated no expectancy, the remaining button were used for different levels of confidence. Participants were instructed to avoid guessing and rely on their feelings of expectancy rather than on explicit memory for the picture. Finally, the picture was presented for 2500 ms. Followed by an ISI between1000 and 2000 ms.

The retrieval phase

Retrieval performance was tested using a cued recall procedure: Each trial started with a fixation cross signalizing the auditory presentation of the word. If participants could remember the associated picture they had to press 'Y' and subsequently type a short description of the content of the picture. If they did not remembered the associated pictures, they pressed 'N' and the next word was presented. Retrieval performance was tested twice: 15 min after the three learning rounds (baseline) and after the 12-hr retention interval (final retrieval). As retention score we calculated the percentage of final retrieval performance with retrieval performance at baseline set to 100%.

Statistical analysis

Data were analyzed using repeated analyses of variance (ANOVA) including the within-subject factor 'emotional arousal' (high vs. low arousing) and the between-subject factors 'sleep/wake' and 'group' (negative pictures group vs. positive pictures group). Post-hoc pair-wise comparisons were conducted using *t*-tests. A probability of $P = 0.05$ was set as significance threshold.

Results

Memory performance at baseline

Consistent with previous studies, during the learning phase we observed a strong advantage of recalling emotional as compared to neutral pictures (emotional memory effect (mean ± SEM): 31.28 ± 1.10 vs. 28.90 ± 1.12 correctly recalled pictures, $t_{71} = 4.65$, $P < 0.001$, d = 0.36, see **Table 2**). The effect was observed both for negative vs. neutral pictures ($P < 0.05$) and positive vs. neutral pictures ($P < 0.001$), although the effect was larger for

positive pictures in our study (significant interaction between the within-subject factor emotional arousal (high vs. low arousing) and the factor 'group' (negative vs. positive picture groups), $F_{(1,68)} = 6.19$, $P = 0.04$, eta² = 0.06).

Table 2: Behavioral data at baseline

		Arousing	Non-arousing	*t*	*P*
All participants					
Cued recall	*Learning*	31.28 ± 1.10	28.90 ± 1.12	4.65	**< 0.001**
Word rating	*Baseline*	2.68 ± 0.12	2.71 ± 0.11	-0.57	0.57
Picture rating	*Baseline*	4.52 ± 0.12	2.45 ± 0.10	13.60	**< 0.001**
Negative Pictures Group					
Cued recall	*Learning*	29.21 ± 1.56	27.86 ± 1.59	2.06	**0.047**
Word rating	*Baseline*	2.97 ±0.17	3.0 ± 0.16	-0.36	0.72
Picture rating	*Baseline*	5.01 ± 0.17	2.38 ± 0.14	15.69	**< 0.001**
Positive Pictures Group					
Cued recall	*Learning*	33.35 ± 1.56	29.94 ± 1.58	4.50	**< 0.001**
Word rating	*Baseline*	2.38 ± 0.16	2.42 ± 0.16	-0.44	0.66
Picture rating	*Baseline*	4.02 ± 0.17	2.51 ± 0.14	6.87	**< 0.001**

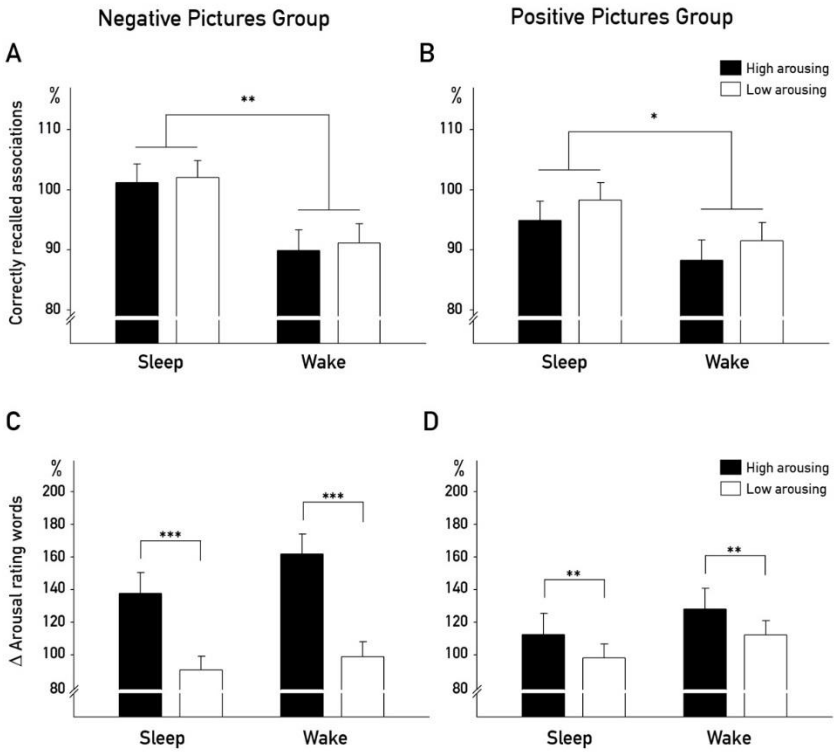
Numbers indicate absolute values of correctly recalled pictures after presentation of the word (of total 50) or arousal ratings (on a 7-point Likert-scale) prior to the retention interval. Data are means ± SEM.

Importantly, cued recall of word-picture pairs at baseline before the retention interval did not differ between sleep and wake groups (30.75 ± 1.46 vs. 29.43 ± 1.61 pictures, $t_{71} = 0.53$, $P = 0.60$), rendering circadian confounds rather unlikely. Descriptively, participants in the 'negative pictures group' generally recalled fewer pictures as compared to the 'positive pictures group', although this effect did not reach statistical significance (56.42 ± 3.21 vs. 63.5 ± 2.87 pictures, $t_{71} = -1.63$, $P = 0.104$, d = 0.39). No further interactions were observed (all $P > 0.70$).

Sleep benefits memory consolidation of word-picture pairs

Consistent with a beneficial role of sleep for memory consolidation, participants who slept after learning exhibited a significantly improved cued recall performance after the 12-hr retention interval as compared to participants who stayed awake after learning: Participants in the sleep groups remembered 99.07 ± 1.80% of the learned word-picture pairs (with learning performance before sleep set to 100%), whereas participants in the wake groups recalled only 90.19 ± 1.96% ($F_{(1,68)}$ = 11.17, $P < 0.001$, eta² = 0.14, see **Table 3**).

Figure 2: *Behavioral results*



A + B Changes in cued recall performance. After a retention interval filled with sleep, participants were significantly better in recalling word-picture associations as compared to participants who stayed awake after learning (main effect of sleep vs. wakefulness; $P < 0.001$, eta² = 0.14). However, the sleep benefit was not selective for associations with high emotional arousal, but similarly occurred for emotional pictures (high arousing, *black bars*) and neutral pictures (low arousing, *white bars*). In addition, the general sleep benefit was not affect by emotional valence (positive vs. negative pictures) and was similarly visible in both picture groups. Changes in cued recall performance are indicated as percentage of recalled associations with performance before the retention interval set to 100%. **C + D** Changes in arousal ratings of neutral words. Words that were associated with high arousing pictures during the learning phase were rated overall as more arousing as compared to words with low arousing picture associations after the 12-hr retention interval. No main effect or interaction with sleep vs. wakefulness was observed. Changes in arousal ratings are indicated as percentage of ratings giving at the end of the experimental procedure, with arousal rated before the learning phase set to 100%. Values are mean ± SEM. $^{**}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$

However in contrast to the notion of a selective effect of sleep on emotional memory consolidation, both emotional and neutral word-picture associations profited equally from a retention interval filled with sleep: While cued recall for emotional pictures was improved by ca. 9% after sleep as compared to the wake group (see **Figure 2**; 98.01 ± 2.23% vs. 89.06 ± 2.42%, respectively, t_{70} = 2.75, P = 0.008, d = 0.65), we observed a comparable improvement of ca. 9% for neutral pictures (100.13 ± 2.03% vs. 91.32 ± 2.20%, for sleep and wake groups, respectively t_{70} = 2.99 , P = 0.004, d = 0.75). Consequently, we observed no significant interaction between the factor sleep/wake and the within-subject factor emotional arousal (high vs. low arousing pictures; $F_{(1,68)}$ = 0.002, P = 0.97). Similarly, we observed no significant interaction with the between-subject factor 'group' (negative vs. positive pictures group, $F_{(1,68)}$ = 0.682, P = 0.41). Interestingly, memory consolidation of associations between words and emotional pictures did generally not differ from consolidation of neutral word-picture associations (main effect of emotional arousal: 93.54 ± 1.65% vs. 95.73 ± 1.50%, respectively, $F_{(1,68)}$ = 1.70, P = 0.197, eta² = 0.024). Our findings indicate that sleep strongly and robustly benefits cued recall of word-picture associations regardless of the emotional arousal and valence of the pictures.

Sleep does not affect generalized emotional arousal of words

Before the emotional association task, arousal ratings of neutral words that were later associated with emotional pictures did not differ from those words that were later associated with neutral pictures (on a 7-point scale: 2.68 ± 0.12 vs. 2.71 ± 0.11, t_{71} = -0.57, P = 0.57, higher numbers indicate higher subjective arousal ratings). This was true for all four groups (see **Figure 2 C + D** and **Table 2**, for descriptive values). After the whole procedure (including the associative emotional memory task, the retention interval and the final retrieval test), words associated with emotional pictures were rated as more arousing as compared to words paired with neutral pictures (134.91 ± 6.68% vs. 99.98 ± 4.34%; t_{71} = 4.03, P < 0.001, d = 0.71) with arousal rating at baseline set to 100%). The effect was stronger for those

words associated with negative as compared to positive pictures ($F_{(1,70)}$ = 4.58, $P < 0.04$, see **Table 3**), which fits well with our result that participants perceived negative pictures as more arousing. This result indicates that participants successfully associated words with the emotional vs. neutral pictures, and that the arousal effects generalized to arousal ratings of the word alone (without picture presentation). However, changes in arousal ratings of words associated with emotionally arousing pictures did not significantly differ between sleep and wake groups (125.01 ± 9.05% vs. 144.80 ± 9.84%; $F_{(1,68)} = 2.39$, $P = 0.13$, see **Table 3**).

Table 3: Change in behavioral data after retention interval

		Sleep	**Wake**	***t***	***P***
All participants		*N = 39*	*N = 33*		
Cued recall	*All pictures*	99.07 ± 1.80	90.19 ± 1.96	3.51	**0.001**
	Arousing	98.01 ± 2.23	89.06 ± 2.42	2.75	**0.008**
	Non-arousing	100.13 ± 2.03	91.32 ± 2.20	2.99	**0.004**
Word rating	*All pictures*	109.76 ± 6.73	125.13 ± 7.32	-1.46	0.15
	Arousing	125.01 ± 9.05	144.80 ± 9.84	-1.39	0.17
	Non-arousing	94.50 ± 5.88	105.46 ± 6.31	-1.30	0.20
Negative Pictures Group		*N = 20*	*N = 16*		
Cued recall	*All pictures*	101.58 ± 2.51	90.51 ± 2.81	2.63	**0.01**
	Arousing	101.15 ± 3.11	89.85 ± 3.48	2.01	**0.05**
	Non-arousing	102.00 ± 2.83	91.16 ± 3.16	2.64	**0.01**
Word rating	*All pictures*	114.21 ± 9.39	130.31 ± 10.51	-1.15	0.26
	Arousing	137.56 ± 12.63	161.74 ± 12.13	-1.21	0.27
	Non-arousing	90.87 ± 8.21	98.86 ± 9.17	-0.92	0.36
Positive Pictures Group		*N = 19*	*N = 17*		
Cued recall	*All pictures*	96.56 ± 2.58	89.88 ± 2.72	2.28	**0.03**
	Arousing	94.86 ± 3.19	88.27 ± 3.37	1.94	**0.06**
	Non-arousing	98.26 ± 2.90	91.48 ± 3.07	1.56	**0.13**
Word rating	*All pictures*	105.29 ± 9.64	119.96 ± 10.19	-0.92	0.35
	Arousing	112.46 ± 12.96	127.87 ± 12.70	-0.87	0.39
	Non-arousing	98.13 ± 8.42	112.05 ± 8.90	-0.93	0.36

Numbers indicate change of correctly recalled associations or change in arousal ratings for words. Change is in percentage (%) and refers to the relative difference from prior to after the retention interval, while the first recall / rating is set to 100%. Therefore a value < 100 % indicates a decrease and a value > 100 % an increase across the retention interval. Data are means ± SEM.

Discussion

Our results indicate that recall of word-picture associations profit strongly from retention periods filled with sleep. Thus, we successfully validated sleep-dependent memory consolidation in our associative emotional memory paradigm. In addition, emotion modulated memory in this task, as cued recall for emotional pictures (negative and positive) was generally increased as compared to neutral pictures. However, we were not able to replicate a selective benefit of sleep on emotional as compared to neutral associations. Sleep generally improved cued recall performance of word-picture pairs, independent of the emotional arousal and valence of the to-be-associated pictures. The latter finding contradicts previous studies reporting a preferential consolidation of emotional memories during sleep (Holland & Lewis, 2007; Payne & Kensinger, 2010). Most of these studies used either single-item memory of pictures (Hu et al., 2006; Kaestner et al., 2013; Nishida et al., 2009) or emotional modulation by incidentally learned emotional contexts (i.e., background image, stories etc., (Payne et al., 2008; Payne et al., 2015; Wagner et al., 2001)). In our study, participants were explicitly told to learn associations between neutral words and emotional as well as neutral pictures. Furthermore, participants were informed that these associations would be tested after sleep. Thus in our paradigm, also associations with neutral pictures are relevant for future behavior, and it might be possible that such a tagging with future relevance overrides selective consolidation of sleep for emotional memories. In a recent study, Groch and colleagues (Groch, Zinke, Wilhelm, & Born, 2014) tried to disentangle the effects of future relevance and emotional memory on sleep-dependent memory consolidation. They reported that while consolidation of emotional memories depends on REM sleep, memories with future relevance are mainly consolidated during NREM sleep. As we did not record polysomnography in our study, future studies need to examine possible shifts in sleep-stage dependencies for consolidation processes related to the associative emotional memory task.

A further limitation of our study is that we did not control for possible differences in circadian time of the learning and retrieval phases between our sleep and wake groups. However, immediate recall performance did not significantly differ between the two groups, suggesting that encoding success is comparable for participants performing on the task either in the morning or in the evening. Similarly, arousal ratings of pictures did not depend on circadian time. Although it cannot be assumed that circadian time has in general no effect on memory processes, we consider a confounding influence in this study on arousal ratings and cued recall performance rather unlikely.

As expected for the associative memory task, arousal ratings for words associated with emotional pictures increased during the course of learning. However, the change in arousal ratings after the 12-hr retention interval did not significantly differ between the 'sleep' and 'wake' group. A recent model proposed that sleep does not only strengthens the content of emotional memories but also reduces its associated affective tone (Walker & van der Helm, 2009). Evidence for this model is quite inconsistent, as studies have reported a role of sleep in depotentiation (Cunningham et al., 2014; Pace-Schott et al., 2011) , but also a protection (Baran, Pace-Schott, Ericson, & Spencer, 2012; Groch, Wilhelm, Diekelmann, & Born, 2013), or even potentiation (Lara-Carrasco, Nielsen, Solomonova, Levrier, & Popova, 2009; Wagner, Fischer, & Born, 2002) of emotional reactivity to arousing stimuli. Our findings add to this literature by showing that changes in generalized arousal ratings after learning of emotional associations are not differentially affected by sleep or wakefulness after learning.

To conclude, our results indicate that the consolidation of word-picture pairs in the associative emotional memory task profits from retention intervals filled with sleep. Thus, the task is suitable for examining potential mechanisms underlying processes of memory consolidation during sleep. In particular, the task can be used to induce reactivation of emotional vs. neutral memory association by verbal cueing during sleep. However, future studies

are necessary to directly compare possible moderators of the selectivity of sleep for consolidating memories with a high future relevance.

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III. Emotional arousal modulates oscillatory correlates of targeted memory reactivation during NREM, but not REM sleep

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Abstract

Rapid eye movement (REM) sleep is considered to preferentially reprocess emotionally arousing memories. We tested this hypothesis by cueing emotional vs. neutral memories during REM and NREM sleep and wakefulness by presenting associated verbal memory cues after learning. Here we show that cueing during NREM sleep significantly improved memory for emotional pictures, while no cueing benefit was observed during REM sleep. On the oscillatory level, successful memory cueing during NREM sleep resulted in significant increases in theta and spindle oscillations with stronger responses for emotional than neutral memories. In contrast during REM sleep, solely cueing of neutral (but not emotional) memories was associated with increases in theta activity. Our results do not support a preferential role of REM sleep for emotional memories, but rather suggest that emotional arousal modulates memory replay and consolidation processes and their oscillatory correlates during NREM sleep.

Introduction

Emotional events are highly relevant for adaptive behavior and therefore better encoded and remembered than neutral ones (LaBar & Cabeza, 2006). According to the widely accepted memory modulation hypothesis (McGaugh, 2004), activation of the amygdala by emotions during encoding modulates plastic processes in memory-related brain regions including the hippocampus, thereby increasing subsequent consolidation processes. In support of this notion, emotionally arousing learning material is better remembered than neutral stimuli (Kensinger, 2009), and this emotional memory advantage increases over time (Anderson, Yamaguchi, Grabski, & Lacka, 2006; Sharot & Yonelinas, 2008), suggesting a continuing influence of emotional arousal on ongoing consolidation processes.

In addition to emotional arousal, sleep has also been critically implicated in the consolidation of memories. The beneficial effect of sleep on memory occurs presumably due to a spontaneous reactivation of newly encoded memories during sleep (Rasch & Born, 2013). According to the active system consolidation hypothesis (Diekelmann & Born, 2010), hippocampal memory reactivations during Non-rapid eye movement (NREM) sleep support the strengthening and integration of memories into cortical long-term stores. Several authors have suggested that this replay process during sleep is selective, thereby specifically strengthening those memories that are relevant for our future behavior (Diekelmann, Wilhelm, & Born, 2009; Walker & Stickgold, 2010). Supporting this concept, sleep selectively strengthens those memories associated with reward or expected to be of future relevance (Chambers & Payne, 2014; Groch et al., 2011). Importantly, several studies have reported a preferential or even selective benefit of sleep for emotional memories (Payne et al., 2015). And while rewarded memories seem to be preferentially replayed during NREM sleep (Lansink, Goltstein, Lankelma, McNaughton, & Pennartz, 2009), direct evidence for the preferential replay of emotional memories during sleep in humans is still lacking.

The stage of REM sleep has been long considered of high importance for the consolidation of emotional memories. Dream reports from REM sleep are often vivid and highly emotional(Suzuki et al., 2004) and their content is potentially involved in memory reprocessing (Fosse, Fosse, Hobson,

& Stickgold, 2003; Nielsen & Stenstrom, 2005; Siegel & Siegel, 2009). Moreover, several empirical studies have provided evidence for a critical role of REM sleep for emotional memories: A growing body of research in rodents consistently shows that REM sleep increases after an emotional learning task (e.g. fear conditioning (Smith, 2011)). In some cases, however, fear conditioning produced a selective suppression of subsequent REM sleep (Liu, Tang, & Sanford, 2003; Sanford, Tang, Ross, & Morrison, 2003). In humans, studies using the night-half paradigm show that emotional memories are particularly strengthened after late-REM sleep rich sleep (Cahill & McGaugh, 1998; Groch, Wilhelm, Diekelmann, & Born, 2013; Menz, Rihm, & Buchel, 2016; Wagner, Gais, & Born, 2001) and higher amounts of REM sleep predict increased emotion memory performance(Nishida, Pearsall, Buckner, & Walker, 2009) and their neural correlates (Menz et al., 2013; Spoormaker et al., 2012). On a theoretical level, it has been proposed that REM sleep represents a neurobiological brain-state particularly beneficial to selective emotional memory processing (Hu, Stylos-Allan, & Walker, 2006; Walker, 2009; Walker & van der Helm, 2009): For example, limbic regions including the amygdala show increased activity during REM sleep (Maquet, 1995; Maquet & Franck, 1997), which might reflect a reactivation of emotionally salient memories during REM sleep (Sterpenich et al., 2009). Furthermore, increased cholingeric activity during REM sleep might enhance amygdala-dependent memory reprocessing (Walker & van der Helm, 2009). In addition, characteristic theta oscillations during REM sleep have been linked to the consolidation of emotional memories (Boyce, Glasgow, Williams, & Adamantidis, 2016). Theta rhythm might coordinate the replay of emotional memories in different brain regions that were initially involved in encoding various aspects of emotional experiences (Goldstein & Walker, 2014; Nishida et al., 2009) and promote their integration into pre-existing autobiographical memory networks (Cahill, 2000; Deliens, Gilson, & Peigneux, 2014; Jones & Wilson, 2005). Finally, the entire process of emotional reprocessing during REM sleep might possibly be related to dreaming activity during this sleep stage (Walker & van der Helm, 2009). In spite of this theoretical assumption, a causal role of memory reactivations during REM sleep for emotional memory consolidation has not yet been shown. Replay processes during REM sleep have been observed in rodents (Louie & Wilson, 2001) but it remains unclear whether they serve the same

function as during NREM sleep (Bendor & Wilson, 2012) or if they are exclusively beneficial for emotional memories.

An established technique to examine this questions is targeted memory reactivation (TMR) during sleep, which consists of inducing reactivation by presenting memory cues during sleep (Oudiette & Paller, 2013). Using TMR, it has been consistently shown that re-exposure to memory cues during NREM (but not during REM) sleep improves neutral declarative memory consolidation (Cairney, Durrant, Hulleman, & Lewis, 2014; Cordi, Diekelmann, Born, & Rasch, 2014; Fuentemilla et al., 2013; Rasch, Büchel, Gais, & Born, 2007; Rudoy, Voss, Westerberg, & Paller, 2009; Schreiner & Rasch, 2014). In addition, we could show by using verbal memory cues that the strengthening of memories by cueing is associated with an increase in theta as well as spindle activity during NREM sleep (Schreiner, Lehmann, & Rasch, 2015; Schreiner & Rasch, 2014). Studies using TMR for emotional memories are scarce and reveal quite inconsistent results. In rodents, repeated presentation of conditioned cues during sleep increases fear memories during both REM (Hars, Hennevin, & Pasques, 1985) and NREM sleep (Barnes, Chapuis, Chaudhury, & Wilson, 2011; Hennevin, Huetz, & Edeline, 2007; Rolls et al., 2013). In humans, reactivating fear condition memories during NREM reduced memory for fear (Hauner, Howard, Zelano, & Gottfried, 2013), while inducing reactivations of fear memories or emotional faces during REM sleep had no effect (Cairney et al., 2014; Rihm & Rasch, 2014; Sterpenich et al., 2014). A possible reason for inconsistent results might be that no study so far systematically compared reactivation success for emotional memories during (deep) NREM and REM sleep. In addition, the oscillatory correlates of successful emotional memory reactivation during sleep are still completely unclear.

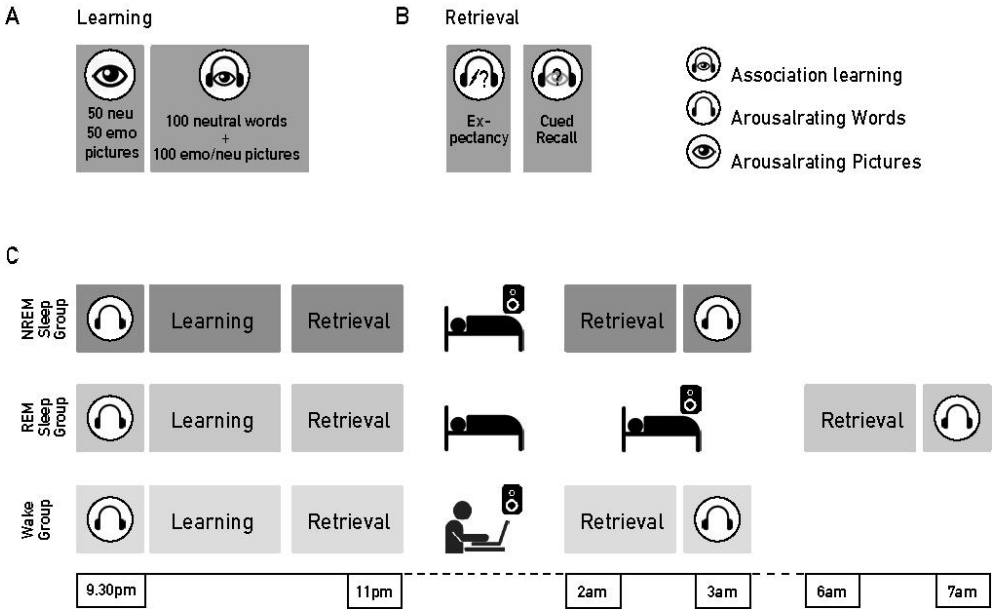
Here we systematically tested the effect of cueing memories during REM and NREM sleep as well as wakefulness on emotional memory formation. We hypothesized that TMR of emotionally arousing memories during REM sleep selectively improves emotional memories associated with increases in oscillatory theta activity. In addition, the benefits of cueing emotional memories during REM sleep should exceed the cueing benefits obtained during NREM sleep. In contrast to our hypotheses, our results show that TMR robustly induced a preferential cueing benefit for emotionally

arousing memories during NREM sleep, which was associated with increased theta and spindle activity. During REM sleep, we observed no cueing benefit for emotional memories, only a trend for improved emotional memory consolidation in a subcategory of emotional memories, comprising the most arousing associations. This was, however, not paralleled by increases in theta and spindle oscillations. Our results do not support a specific role for reactivations during REM sleep for emotional memory consolidation, but rather suggest that emotional arousal modulates reactivation processes underlying declarative memory consolidation during NREM sleep.

Results

We tested our hypotheses using a newly developed emotional associative learning task: Sixty-two healthy young participants learned to associate spoken neutral words with a picture shown on a computer screen. The learning material consisted of 100 neutral words of which 50 words were associated with emotionally arousing pictures and the remaining 50 words were associated with neutral pictures. From each category, emotional and neutral, half of the words were randomly and repeatedly presented either during NREM sleep (n = 21), REM sleep (n = 20) or wakefulness (n = 21), in a between-subject design. Cued recall was tested after the retention interval, during which each word was presented auditory and participants were asked to write down a short description of the associated picture (see **Figure 1**, for a summary of the experimental procedure and design).

Figure 1: Experimental Procedure

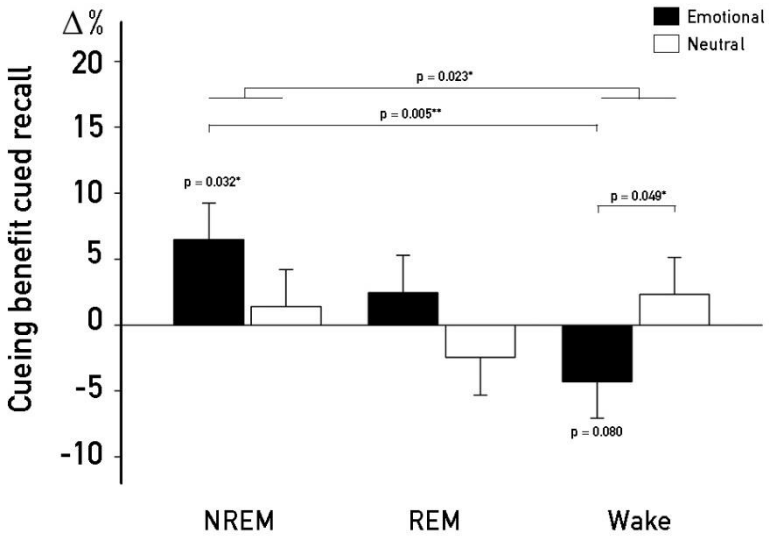


A Before learning, all participants first rated the arousal of 100 neutral words and 50 arousing (emotional, emo) and 50 non-arousing pictures (neutral, neu), respectively. Then they performed on the emotionally association learning task. In this task, first a neutral word was presented via loudspeakers, followed by the presentation of an emotionally arousing or neutralpicture. The same word was presented a second time during the picture presentation. Participants performed on three rounds: No response was required in the first round. In the second and third round, participants rated the expectancy of an arousing pictures after the first presentation of the word. In any case, following the rating the correct picture was presented again serving as feedback. **B** During retrieval, participants heard the word and had to indicate the expectancy of an arousing picture (Expectancy) and provide a brief written description of the picture (Cued Recall). **C** Retrieval performance was assessed immediately after learning and after the retention interval. During the 3-h (NonREM Sleep and Wake Group) or 6-h retention interval (REM Sleep Group), single word cues were presented repeatedly for 80 minutes via loudspeakers, either during NREM, REM or during performance of a computer working memory task. At the end, subjects rated the arousal level of words again.

Retention performance and cueing benefits.

To test our main hypothesis, we analyzed the benefits of cueing during different brain states (NREM, REM and wake) on memory for emotionally arousing and neutral associations using a 3x2 analysis of variance. As dependent variable we used the cueing benefit score (correctly recalled cued minus uncued associations, with learning performance set to 100%). As expected, only in the NREM sleep group, cueing benefits were significantly different from zero, i.e. cued associations were better remembered than uncued associations (NREM: $P = 0.032$, REM: $P = 0.982$; Wake: $P = 0.692$, see **Figure 2**).

Figure 2: Cued Recall



Differences in cueing benefits for emotional and neutral associations. Cueing of emotional associations (black bars) improved memory recall only when applied during NREM ($P = 0.032$), but not during REM sleep or wakefulness. Cueing benefits for emotional associations were greater for the NREM ($P = 0.01$) as compared to the Wake group. Independent of arousal, cueing benefits were generally greater for the NREM as compared to the Wake group (main effect of cueing: $P = 0.037$), while no general cueing benefit emerged for REM sleep ($P = 0.84$). The cueing benefit score was created by first calculating the change of correctly recalled associations for cued and uncued associations separately, with setting the performance before the retention interval to 100%. Following, the uncued was subtracted from the cued score. Values are mean ± SEM. $*P \leq 0.05$ $**P \leq 0.01$.

Moreover, we observed a significant interaction between "group" and "emotional valence" ($F_{1,59} = 3.17$, $P = 0.049$, $\eta_p^2 = 0.102$), which was mainly driven by a significantly greater cueing benefit for emotionally arousing associations after cueing during NREM sleep as compared to wakefulness (planned post-hoc pairwise comparison for emotional associations: NREM vs. wake: $t_{1,40} = 2.95$, $P =$

0.005, η_p^2 = 0.17, REM vs. wake: $t_{1,39}$ = 1.75, P = 0.088, η_p^2 = 0.07; NREM vs. REM: $t_{1,39}$ = 0.96, P = 0.343, η_p^2 = 0.02, see **Figure 2**). However, cueing of neutral associations did not benefit memory performance in any group (all $P \geq 0.26$). Memory performance for uncued associations did not differ between the NREM and the REM sleep group ($t_{1,39}$ = 1.18, P = 0.244), indicating that the longer sleep duration for the latter (see **Table 2**) did not influence general memory consolidation of associated pictures in our task.

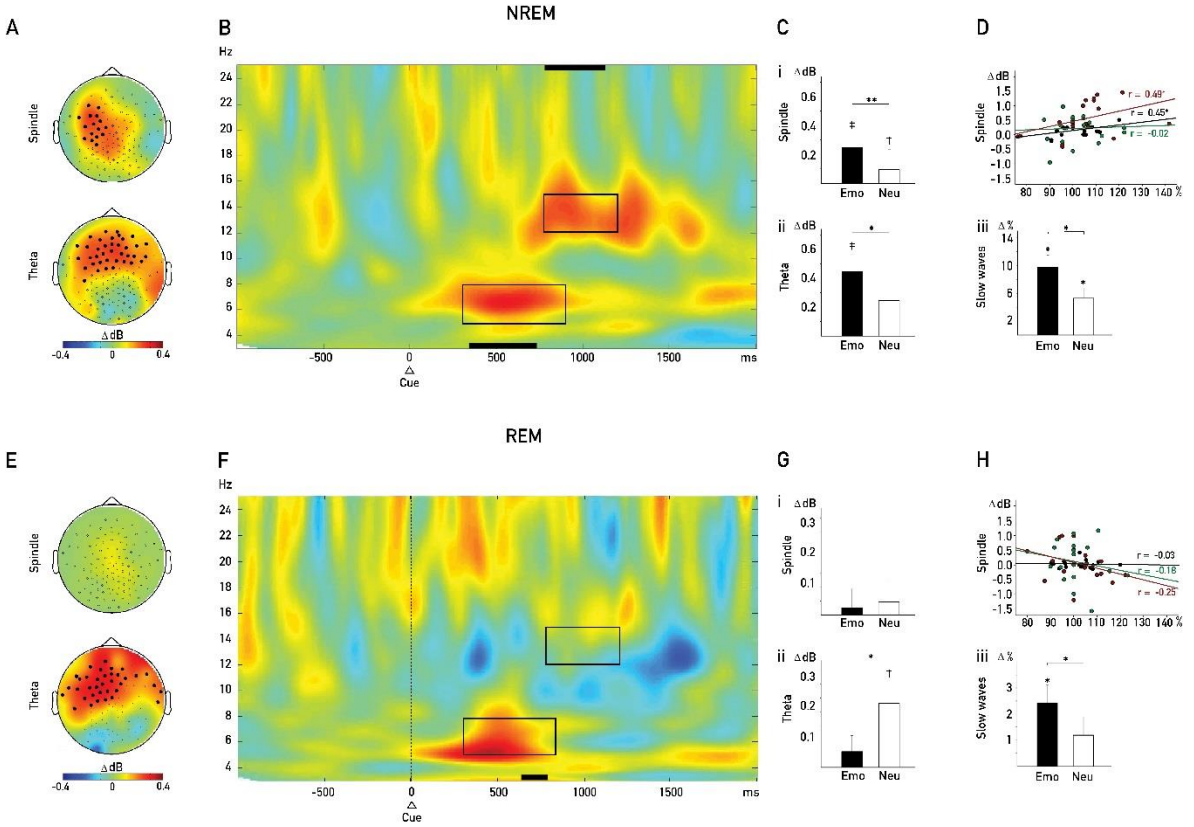
Descriptively in the wake group, cueing of high arousing association impaired memory performance, while this "negative cueing benefit" did not reach significance (P = 0.080). For neutral associations, no significant effects emerged (all $P \geq 0.20$).

As opposed to cued recall performance, expectancy ratings for high and neutral associations were not affected by cueing, irrespective whether it occurred during NREM, REM or wakefulness ($F_{2,59}$ = 0.50, P = 0.61). Analyzing the three groups separately revealed no sleep stage specific cueing, emotional arousal or interaction effect on expectancy ratings (all $P > 0.37$; see **Supplementary Table 3** for details). For a detailed description of the baseline memory performance and arousal ratings, see *Supplementary Materials* and **Supplementary Tables 1-3**.

Oscillatory correlates of successful memory cueing during sleep

We focused on the analysis of oscillatory activity in the theta and spindle range associated with successful memory cueing during sleep based on our previous findings during NREM sleep (Schreiner, Lehmann, et al., 2015; Schreiner & Rasch, 2014). We defined successful memory cueing as the difference between oscillatory responses for verbal cues presented during sleep for which the associated picture was later remembered vs. forgotten (subsequent cueing effect, SCE). Building upon those prior findings mentioned above, induced theta power (5-8 Hz) was analyzed between 300 and 900 ms, induced spindle power (12-15 Hz) between 800 –1200 ms. First, we analyzed whether we could replicate our previous findings in the NREM group, before then extending the analysis to REM sleep.

Figure 4: Oscillatory Analyses



Results for oscillatory analysis in the theta (5-8 Hz) and spindle band (12-15 Hz) in the NREM and REM group. Oscillatory activity after word replay (dotted line in **B and F**) was analyzed for *subsequently remembered* and *subsequently not remembered* trials. **NREM group (A-F): A** Significant cluster of electrodes in the spindle and theta band. **B** Time frequency plot for the overlap of significant electrodes of the theta and spindle cluster (black and white dots in **A** upper topoplot). Differences in power of theta and spindle activity were statistically tested for the electrodes shown in **A** and the time window (theta band: 300-900ms and spindle band: 800-1'200ms) and frequency range as illustrated in the rectangles in **B**. For both, spindle **(C)** and theta **(E)**, the difference in power between *subsequently remembered* and *subsequently not remembered* (ΔdB) was significantly different from zero for emotional and neutral trials. The increased power in the theta and spindle band was significantly more pronounced in emotional as compared to neutral trials. The increase in spindle activity **(D)** after cueing of *subsequently remembered* (black dots) trials correlated significantly with improved memory performance in the cued recall test. The correlation was stronger for *emotional* (red dots) and did not reach significance for *neutral* trials (green dots). Furthermore, the cues of *subsequently remembered* trials were followed by more slow waves **(F)** as compared to *subsequently not remembered* trials (represented by zero). Within the remembered trials, slow waves occurred more often in emotional as compared to neutral trials. In the **REM group (G-L)**, power in the theta band for subsequently remembered trials was increased for the same time and frequency window **(H)** over the same cluster as in the NREM group **(G)**. The enhanced power the theta band **(K)** for *subsequently remembered* as compared with *subsequently not remembered* (ΔdB) was significantly more pronounced in *remembered* neutral as compared with *remembered* emotional trials. Spindle power **(I)** did not differ between the conditions in the REM group, and neither the increase in spindle **(J)** nor theta power (not shown here) did correlate with memory performance. The cueing of *subsequently remembered* trials was associated with more slow waves **(L)** as compared to *subsequently not remembered* trials (represented by zero). Within the remembered trials, slow waves occurred marginally more often after emotional as compared to from neutral trials. The slow wave score was created by first calculating the percentage of trials that were followed by a slow wave, separately for *subsequently remembered* emotional and neutral and not remembered trials. Following, the percentage for *subsequently not remembered* was subtracted from the score for remembered trials. Changes in cued recall performance are indicated as percentage of recalled associations with performance before the retention interval set to 100%. Values are mean ± SEM. $*P < 0.05$, $**P < 0.01$.

As expected, we observed a significant SRE for both theta and spindle activity during NREM sleep: Theta power was significantly higher after verbal cues for which the associated pictures were later remembered vs. forgotten in a bilateral frontal electrode cluster ($P = 0.014$, corrected for multiple comparisons, see **Fig. 3A** (lower panel) and **3B**). Similarly, several electrodes that were mostly left lateralized over central regions showed a positive SRE for induced spindle power ($P = 0.04$, corrected for multiple comparisons, see **Fig. 3A** (upper panel) and **3B**). This two electrode clusters were used as region of interests (ROIs) for all subsequent analyses.

In a second step, we extracted oscillatory power within the respective ROIs for later remembered emotional associations and later remembered neutral associations separately. The later forgotten category was not divided by arousal due to a low number of trials in the emotional category. During NREM sleep, theta and spindle oscillatory power nicely reflected the behavioral result pattern with respect to cued recall performance: We observed a significantly higher response in both spindle and theta activity after later remembered cues that were associated with emotionally arousing pictures as compared to neutral pictures (theta: $t_{19} = 2.20$, $P = 0.040$, $\eta_p^2 = 0.02$; spindle: $t_{19} = 2.69$, $P = 0.014$, $\eta_p^2 = 0.04$, see **Fig. 3C**). In addition, while cueing of later remembered emotional associations induced a significant increase in theta ($t_{19} = 2.85$, $P = 0.010$, $\eta_p^2 = 0.02$) and spindle activity ($t_{19} = 3.94$, $P = 0.001$, $\eta_p^2 = 0.06$) as compared to subsequently forgotten associations, this power increase for remembered was only observable in spindle ($t_{19} = 2.25$, $P = 0.037$, $\eta_p^2 = 0.03$) but not theta range ($t_{19} = 1.22$, $P = 0.22$; see **Fig. 3C** and **Supplementary Fig. 2A**). The improvement in overall cued recall performance in the NREM sleep group was positively correlated with cueing induced spindle power ($r = 0.45$, $P = 0.04$, **Fig. 3D**) but not with theta power ($r = -0.03$, $P = 0.82$, not shown) after cueing. Fitting well with the previous findings, the correlation was more robust for emotional ($r = 0.49$, $P = 0.01$) and was not significant for neutral trials ($r = -0.02$, $P = 0.921$: see **Fig. 3D** for spindle power). The correlation was marginally stronger for higher for emotional as compared to neutral associations ($P = 0.047$) and the reached almost significance when comparing Emotional+ and neutral associations ($P = 0.055$, not shown here).

During REM sleep oscillatory responses for cues for which the associated picture was later remembered vs. forgotten differed only in the theta but not spindle range (see **Fig. 3E** and **3F**). When extracting power values using the same (NREM) ROI, we found significantly increased theta activity for later remembered associations (t_{16} = 1.93, P = 0.07, η_p^2 = 0.05). However, in contrast to the behavioral result pattern observed by cueing during REM sleep, verbal cues associated with later remembered neutral pictures induced the strongest increase in theta activity (t_{16} = 2.54, P = 0.022, η_p^2 = 0.15), whereas induced theta activity for cues associated with emotionally arousing pictures did not differ from non-remembered trials (t_{16} = 0.83, P = 0.42, see **Fig. 3K**). In fact, theta power was even significantly smaller for later remembered emotional as compared to neutral associations (t_{16} = -2.61, P = 0.019, η_p^2 = 0.06). Concerning activity in the spindle range during REM sleep, we did not observe any differences between these trials types for the (NREM-) ROI (see **Fig. 3G**, **3H** and **3I**). Conversely, no significant correlations with memory performance were observed during REM sleep (**Fig. 3J**). Analyzing the oscillatory correlates of successful memory cueing also during REM sleep alone revealed the same pattern of results, only in a smaller cluster (for a detailed description, see *Supplementary Materials*).

As slow oscillations have been suggested to play a functional role in consolidating reactivated memories during sleep (Rasch & Born, 2013) , we counted cue presentations that were followed by surface slow waves at frontal electrode sites. Slow waves were defined as waves with a duration of more than 500 ms, exceeding an amplitude of 75 μV and initiating between 0 and 800 ms after stimulus onset. As reported previously (Schreiner, Lehmann, et al., 2015; Schreiner & Rasch, 2014), we observed that the occurrence of slow waves was higher after cueing of later remembered as compared to later not remembered associations during NREM sleep (t_{19} = 4.36, P < 0.001, η_p^2 = 0.57, see **Fig. 3F**). Again paralleling the pattern of results of the behavioral and oscillatory analyses in the NREM sleep group, cueing of later remembered emotional associations was followed by more slow waves as compared to later remembered neutral associations (t_{19} = 3.13, P = 0.005, η_p^2 = 0.11). Remarkably,

we also observed a higher number of slow waves for later remembered as compared to forgotten associations after cueing during REM sleep independent of arousal (t_{16} = 2.28, P = 0.036, η_p^2 = 0.03). In contrast to the findings for theta power, the count of slow waves reflected the behavioral outcomes of the REM sleep group: While cueing of later remembered emotional associations was associated with a higher number of slow waves (t_{16} = 3.42, P = 0.004, η_p^2 = 0.15), cueing of later remembered neutral associations was not (t_{16} = 1.62, P = 0.13, η_p^2 = 0.01), and this difference reached a statistical trend (t_{16} = 1.85, P = 0.083, η_p^2 = 0.01, see **Figure 3L** and **Table 3** for details). Note that REM sleep was scored in spite of cue-elicited slow-waves (see Methods). Thus, cueing success during REM sleep might a least partly depend on successful triggering of slow-waves by the cue.

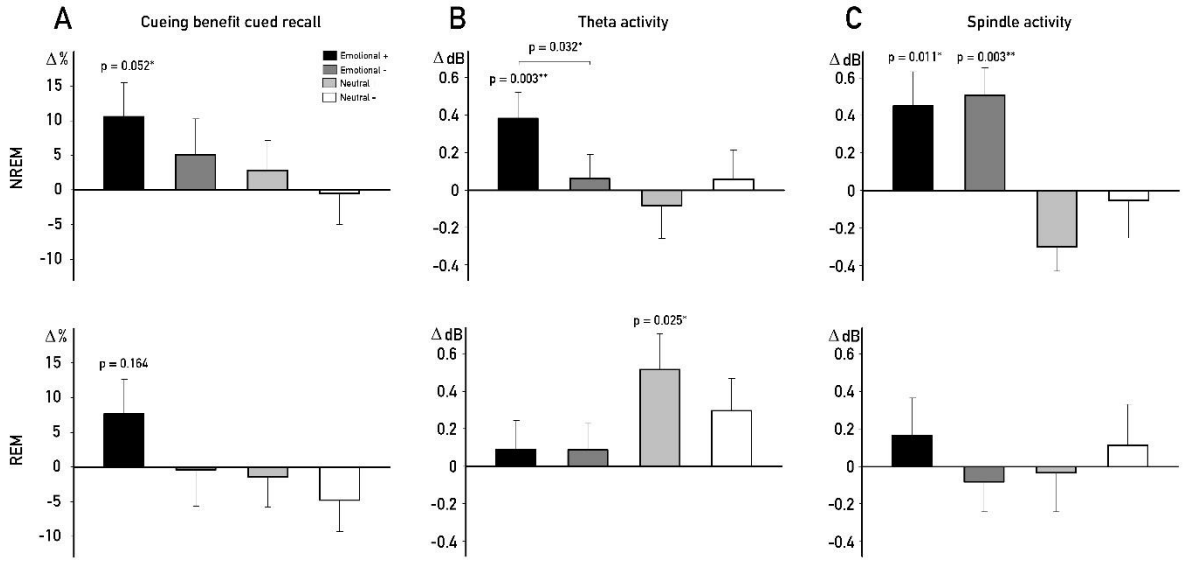
Analyses of subcategories

In an exploratory analysis, we examined whether a more fine-graded categorization of emotionality provides further support of the modulation of cueing effects by arousal levels. The emotional arousal for each picture was defined by individual ratings acquired prior to the associative learning task, and the emotional and neutral picture category were each divided into two equally sized sub-sets. Within the emotional pictures, the 25 pictures rated with the highest emotional arousal were classified as emotionally high (Emotional+) and the remaining 25 pictures as emotionally low arousing (Emotional-). The same subdivision was applied for the neutral pictures, resulting in the categories neutral high (Neutral+) and neutral low arousing (Neutral-).

The cueing benefit within the emotional category was mainly driven by memories for Emotional+ (10.61 ± 3.12 %; $t_{1,20}$= 2.06, P = 0.052, η_p^2 = 0.09, see **Figure 4A**) and not significant from zero for Emotional- (6.51 ± 3.87%; $t_{1,20}$= 0.92, P = 0.368). Interestingly, analyzing the extreme category also in the REM sleep group, revealed that cueing the most arousing associations (Emotional+) was improved memory significantly as compared to waking (P = 0.04), however the cueing benefit was not significantly different from zero (P = 0.16). While it seems that more intense associations tend to benefit from cueing during REM sleep, the difference between Emotional+ and Emotional-

was not significant (7.66 ± 5.01 % vs -0.41 ± 5.27%: $P = 0.33$). Theta activity was only significantly enhanced for Emotional+ ($t_{19} = 2.31$, $P = 0.003$, $\eta_p^2 = 0.08$) and more pronounced for later remembered Emotional+ vs Emotional- ($t_{19} = 2.31$, $P = 0.032$, $\eta_p^2 = 0.08$), mirroring the behavioral findings that cueing of Emotional+ associations was particularly beneficial (see **Figure 4B**). However, spindle activity did not differ between the two emotional categories ($P = 0.69$; see **Figure 4C**).

Figure 3: Cued Recall Power Changes in the four Subcategories



Differences in cueing benefits and oscillatory activity in the theta (5-8 Hz) and spindle range (12-15 Hz) in the NREM and REM group after splitting each, the emotional and neutral category into a high (*Emotional+* and *Neutral+,* respectively*)* and low arousing subcategory (*Emotional-* and *Neutral-,* respectively). Cueing benefits (**A** upper panel) were limited in the NREM group to emotionally high arousing (*Emotional+*) and not observable for emotionally low arousing associations (*Emotional-*). Mirroring this effect, the increase in theta activity for *remembered* trials (**B** upper panel) was mainly driven by the same category but spindle activity (**C** upper panel) was generally increased for remembered emotional association. A trend towards a significant cueing benefit (**A** lower panel) emerged also in the REM sleep ($P = 0.16$) and was restricted to the emotionally high arousing subcategory. Theta power was generally more pronounced in *remembered* neutral as compared with *remembered* emotional trials but the neutrally high (*Neutral+*) and low arousing trials (*Neutral-*) did not differ (**B** lower panel). Spindle power **(C** lower panel**)** was not significantly different for any subcategory and did not differ between the categories in the REM group. The cueing benefit score was created by first calculating the change of correctly recalled associations for cued and uncued associations separately, with setting the performance before the retention interval to 100%. Following, the uncued was subtracted from the cued score. Values are mean ± SEM. $*P \leq 0.05$ $**P \leq 0.01$.

Discussion

For the first time, our study directly contrasted effects of auditory cueing of emotionally arousing memories during deep NREM and REM sleep as well as wakefulness. As expected, cueing benefits were sleep-specific. However, contrary to our hypothesis, we did not find any hint for a preferential and selective cueing benefit during REM sleep for emotional memories. In fact, cueing memories during NREM sleep resulted in a robust preferential strengthening of emotionally as compared to neutral memories. Further corroborating the emotional modulation of cueing, only the high arousing emotional memories benefitted from cueing with a gradual decline of cueing benefit with decreasing arousal. A similar but weaker effect for highly arousing memories was observed during REM sleep, which did not reach statistical significance. During REM sleep might only highly disturbing memories are re-processed and hence consolidated. Future studies, using exclusively stimuli eliciting strong emotional arousal possibly strengthen the effect of cueing during REM sleep.

Our results are in line with the notion that replay during NREM sleep is modulated by emotionality and future relevance of newly encoded stimuli, leading to increased replay of emotionally salient and rewarded stimuli during NREM sleep and improved later recall (Lansink et al., 2008, 2009; Wilhelm et al., 2011). However, our results are not in line with the view that reactivations during REM sleep are functionally relevant for the assumed role of REM sleep in preferential consolidation of emotional memories, particularly as compared to NREM sleep.

Our results from the oscillatory analyses support this conclusion. According to our working model derived from our previous studies with (neutral) vocabulary cueing during sleep(Schreiner & Rasch, 2016), induced theta oscillations reflect the successful reinstatement of the memory trace by cueing. Subsequently, induced spindle oscillations are mandatory for a successful stabilization and strengthening of the memory trace after cueing. The role of sleep spindle oscillations in memory consolidation and plasticity is widely supported (Rasch & Born, 2013). Specifically, hippocampal signals of reactivation are assumed to be nested in individual troughs of spindles (Mölle, Eschenko, Gais, Sara, & Born, 2009; Siapas & Wilson, 1998; Staresina et al., 2015). Furthermore, sleep spindles are thought to prime and maintain long-term potentiation in cortical circuits by provoking Ca^{2+} influx for successive

plasticity associated processes (Contreras, Destexhe, & Steriade, 1997), possibly thereby supporting the redistribution of reactivated memories to cortical long-term memory stores (Born & Wilhelm, 2012).

Unlike spindle power, the involvement of theta activity during NREM sleep for memory consolidation is not yet widely accepted. During wakefulness, theta activity is consistently associated with memory formation and function in a number of species and predicts success of later recall (Klimesch, 1999; Mizuseki, Sirota, Pastalkova, & Buzsàki, 2009). Furthermore verbal cueing during sleep leads to enhanced theta activity during later recognition testing, possibly indicating the presence of a stronger memory trace (Schreiner, Göldi, & Rasch, 2015). It is assumed that theta activity is crucial for binding information together, particularly binding information from disparate brain regions during encoding and retrieval (Lisman & Jensen, 2013; Vertes, 2005). During sleep, increased theta power is also associated with better memory consolidation in healthy participants and patients (Schabus, Hodlmoser, Pecherstorfer, & Klosch, 2005; Westerberg et al., 2012). In the present study, successful cueing of emotional and neutral pictures during NREM sleep elicited both increased theta and spindle activity, replicating our previous finding from vocabulary learning also in terms of timing and topography (Schreiner, Lehmann, et al., 2015; Schreiner & Rasch, 2014). Importantly, the subsequent cueing effect (SCE) during NREM sleep differed solely quantitatively, but not qualitatively between emotionally arousing and neutral memories: Successful cueing of emotional pictures revealed a stronger increase in theta and spindle oscillations as compared to neutral pictures, thereby paralleling the improvements by cueing for emotional vs. neutral pictures on the behavioral level. In addition, the increase in induced spindle power was positively correlated with the individual retention performance.

In contrast, during REM sleep, we did not observe increased theta activity during the successful cueing of emotional memories or the subcategory of memories eliciting a strong arousal, in spite of the trend for behavioral improvements after cueing during REM sleep. For neutral memories, an increase in theta oscillations was observed during REM sleep without any improvements of the behavioral level. Furthermore, cueing during REM sleep did not elicit any activity in the spindle

range, neither for emotional nor neutral memories. Evidence that auditory stimuli are processed during REM sleep comes from the observation that dream content can be modified by presenting words during REM sleep (Berger, 1963; Hoelscher, Klinger, & Barta, 1981). In spite of this successful reinstatement by presenting memory cues during this sleep stage, cued memories are not stabilized during REM sleep, probably because of the missing spindle activity and associated plastic processes.

On the behavioral level, we did not find any effect of TMR during REM sleep on arousal ratings. This contradicts the assumption that replay of emotional memories during REM sleep by affects the arousal component of emotional memories as stated by the sleep-to-remember – sleep-to-forget hypothesis (Walker & van der Helm, 2009). In addition, we did not find any influence of TMR during REM and NREM sleep on expectancy ratings, a measure typically used in fear conditioning research (Boddez et al., 2013). It remains, however, unclear whether these findings also apply for traumatic memories and studies with a stronger clinical focus are needed. For cued recall, we observed a clear benefit of cueing during NREM sleep for emotionally arousing memories, while the cueing benefit did not reach statistical significance for neutral memories. However, several previous studies have in fact reported significant increases in recall performance after cueing during NREM sleep for neutral memories, including spatial and verbal memories (Oudiette & Paller, 2013; Schreiner & Rasch, 2016). Interestingly, sleep-dependent memory consolidation of neutral memories can become attenuated when emotionally arousing items are included into the learning material (Hu et al., 2006; Payne, Stickgold, Swanberg, & Kensinger, 2008; Wagner et al., 2001; Wagner, Hallschmid, Rasch, & Born, 2006). Thus, it might be possible that the preferential reactivation of emotionally memories during NREM sleep biases the sleep-dependent consolidation processes. In other words, sleep and cueing benefits for neutral memories might be reduced when emotionally arousing memories are learned concomitantly. However, this notion requires further testing.

Arguing against the notion of a distinct role of REM sleep for emotional memories, it has been repeatedly suggested that REM sleep might serve distinct but complementary functions for memory consolidation (Rasch & Born, 2013). For example, Llewellyn & Hobson (Llewellyn & Hobson, 2015) argue that REM memory processing cannot be considered in isolation from the role of NREM and Giuditta and colleagues (Giuditta et al., 1995) suggest that the optimum benefits of

sleep on the consolidation of both declarative and non-declarative memory occur when NREM and REM sleep take place in succession. While NREM reactivates and reorganizes previously acquired memories, REM sleep then might function to support processes of synaptic plastic changes, creating enduring connections for the long-term. Thus, it might be possible that emotionally arousing memories are preferentially replayed during NREM sleep, and then additional memory processes occur during subsequent REM sleep which do not involve replay of memories (or are at least less influenced by targeted memory reactivation).

Another interpretation of our findings is that cueing during REM sleep does not lead to a strengthening of the exact same memory trace, but lead to other memory processes involving generalization or strengthening of previously weaker, far-fetched associations. While cueing during REM sleep had no effect on accurate memory performance in the study by Sterpenich and colleagues (Sterpenich et al., 2014), it increased the number of false positives. In addition, Stickgold and colleagues (Stickgold, Scott, Rittenhouse, & Hobson, 1999) propose that weaker associations are replayed during REM sleep possibly playing a role in creative processes. Interestingly, we observed stronger theta oscillatory power after cueing of neutral compared to emotional memories, in spite of a trend towards a better (accurate) memory recall for emotionally high arousing memories. This "inverse" theta effect possibly reflect a higher success of cueing several rather "far-fetched" memory associations, which are less relevant for accurate remembering but involved in creative processes.

A third alternative interpretation of our findings is that targeted memory reactivations have indeed no effect on memory processes during REM sleep, and that the small but non-significant improvements reported here are due to NREM-like processes occurring during REM sleep. For example, a recent study in mice demonstrated that slow waves, the hallmark of NREM sleep, occur regularly also during REM sleep but only in deeper layers of primary cortical areas (Funk, Honjoh, Rodriguez, Cirelli, & Tononi, 2016), which go undetected in recordings from the scalp. A similar finding has been reported from studies in rats (Vyazovskiy, personal communication). In addition, we observed that several successfully cued memories induced slow waves or K-complexes during REM sleep (note that REM scoring was only continued after the occurrence of an isolated K-complex following the word presentation when (a) the remaining epoch met all criteria for scoring of

REM sleep, (b) rapid eye movements were visible in the same epoch and (c) both the previous and subsequent epoch were unequivocally scored as REM sleep). Thus, it might be possible that targeted memory reactivation during REM sleep recruited (or induced) some NREM sleep like features, which resulted in a weak improvement of emotional memories by cueing. Interestingly, Funk and colleagues (Funk et al., 2016) did not detect sleep spindles during REM sleep. This is consistent with our finding that activity in the spindle range is involved in memory processing only during NREM but not REM sleep. According to this interpretation, targeted memory reactivation for both emotional and neutral memories is only beneficial when cues are either presented during NREM sleep or when they involve NREM-like features during REM sleep.

When memory cues were presented during wakefulness while performing on a working memory task, recall performance was not affected. Considering that effects of cueing during wakefulness do not differ between passive listening and performing on a working memory task (Schreiner & Rasch, 2014, 2015), we can exclude that the working memory task interfered with the processing of the memory cues.

Taken together, our findings provide no evidence for the notion that cueing during REM sleep explains a preferential consolidation of emotionally arousing memories during this sleep stage. In contrast, emotional arousal during encoding modulated oscillatory correlates during NREM in a quantitative rather than qualitative manner, possibly indicating that emotional and neutral (declarative) memories are consolidated by similar mechanisms during NREM sleep. According to this "modulation hypothesis" of memory consolidation during sleep, emotion would result in a preferential replay and consolidation of memories during NREM sleep, which might underlie the observed cueing benefits and increased oscillatory correlates for emotional memories during NREM sleep reported here. Whereas during REM sleep, the occurrence of NREM-like features (i.e. slow waves etc.) might be necessary for inducing memory benefits by targeted memory reactivation during sleep.

Materials and Methods

Participants

Sixty-two subjects participated in the three experimental groups (NREM sleep group: n = 21, REM sleep group: n = 20 and Wake group: n = 21, see **Table 1** for details). Participants were free of any medication at the time of the experiment and none had a history of any neurological or psychiatric disorders. All subjects reported a normal sleep-wake cycle and none had been on a night shift for at least 8 weeks before the experiment. On experimental days, subjects were instructed to get up at 7.00 h and were not allowed to take in caffeine and alcohol or to nap during daytime.

The study was approved by the ethics committee of the Department of Psychology, University of Zurich, and all subjects gave written informed consent prior to participating. After completing the whole experiment, participants received 120 Swiss francs (CHF) (sleep groups) or 100 CHF (wake groups), respectively.

Table 1: Demographic data

	N	Age	m/f
NREM	*21*	22.1 ± 0.5	5/16
REM	*20*	22.3 ± 0.8	4/16
Wake	*21*	23.5 ± 0.6	5/16

Demographic data of the three experimental groups.

General procedure

Participants entered the laboratory at 21.00 h. The session started with the application of the electrodes for standard polysomnography, including electroencephalographic (EEG; 128 channels, Electrical Geodesic, Inc.), electromyographic (EMG), and electrocardiographic (ECG) recordings. Prior to the experiment, participants of the sleep group spent an adaptation night in the sleep laboratory.

In all 3 experimental groups, the learning phase started at ~ 22.00 h with the associative emotional memory task (for details see *The associative emotional memory task*). After completing the

learning task, participants of both sleep groups went to bed at 23.00 h and were allowed to sleep for 3 h (NREM group) or 6h (REM group), respectively whereas participants in the wake control groups stayed awake during 3h (see **Fig. 1**, for an overview of the procedure). During the retention interval, a selection of prior learned words was presented for ~80 minutes during sleep stages N2 and N3 for participants of the NREM group, during stage REM for participants of the REM sleep group and during wake for participants of the wake group, respectively (see below for a detailed description of the cueing phase).

Learning tasks

The associative emotional memory task. The associative emotional memory task consisted of 100 words and pictures, which were grouped into association pairs. The words were two syllable substantives selected from the Berlin Affective Word List Reloaded (Võ et al., 2009), a German database providing normative ratings for emotional valence and arousal. The selection criterion was neutral rating with a very small standard deviation (mean rating 0 ± 0.2 SD on a -3 to +3 scale). In order to provide an auditory presentation, words were read by an actress and recorded in-house (sound file duration: 400-700ms). The set of visual stimuli consisted of 100 pictures taken from the Nencki Affective Picture System (Marchewka, Zurawski, Jednoróg, & Grabowska, 2014) (NAPS). Fifty of these pictures are generally rated as neutral and low arousing. The remaining 50 pictures elicit a high level of emotional arousal and are perceived as negative in emotional valence. The learning material for a single subject consisted therefore of 100 neutral words of which 50 words were associated with emotionally arousing pictures and the remaining 50 words were associated with neutral pictures. The associations between words and pictures were balanced across participants. Since the perception of pictures as arousing can differ dramatically between subjects, we further subdivided the emotional picture set based on individual arousal ratings into two equally sized categories. This resulted in a set of pictures comprising the 25 most arousing pictures ("emotional high arousing") and a picture set comprising the 25 less arousing emotional pictures ("emotional low arousing"). The same procedure

was applied for the neutral pictures, resulting in the two sub-sets "neutral high arousing" and "neutral low arousing".

Arousal ratings. Prior to the associative emotional memory task, participants rated words and pictures separately on a 7-point Likert-scale with respect to the level of arousal, ranging from 'not at all arousing' to 'highly arousing'. Following a fixating cross, displayed for 1,000 ms in the center of the screen, the respective word was presented auditory via head-phones. Subsequently, the rating scale was displayed and subjects were instructed to use the keyboard to indicate the arousal elicited by the stimulus. The rating of the picture followed the same procedure, with pictures being presented on the computer screen for 1,500 ms.

Participants of the study rated emotional pictures as more arousing than neutral pictures (5.31 ± 0.08 vs. 2.23 ± 0.13; $F_{1,59} = 829$, $p < 0.001$, $\eta^2 = 0.753$) with no significant difference between the three groups ($F_{2,59} = 0.113$, $p = 0.87$).

The learning phase. During the associative emotional learning paradigm, participants were instructed to memorize the word-picture pairs. They had to complete a total of three rounds: During the first round, the words were presented auditory after a fixation cross (1,000 ms), followed by visual presentation of the picture on the computer screen. 1,000 ms after picture onset, the respective word was played a second time. The picture was presented for 2,500 ms followed by an inter-stimulus interval (ISI) with a random duration (1,000-2,000 ms). No response was required during the first learning round. During the subsequent two rounds, the first word presentation was again followed by a 7-point Likert-scale and participants had to indicate whether they expected a low or high arousing picture. Subjects were instructed to press '7' (or '1'), if they expected a high (or low, respectively) emotionally arousing picture, with highest certainty. The "medium" button '4' indicated no expectancy, while the remaining buttons were used for graded levels of confidence. Participants were instructed to avoid guessing and to rely on their feelings of expectancy, rather than on explicit memory for the picture. In any case, following the key press the correct picture was presented again for 2000 ms, serving as feedback.

After a delay of 15 min, subjects underwent two types of recall testing. Using the same procedure as during the learning procedure, subjects had to indicate the expectancy of an arousing or non-arousing picture but no feedback was provided in form of the associated picture. Therefore, the response served as an index for successful implicit memory formation. In contrast to the cued recall test, expectancy ratings require only the anticipation of an event and no explicit or detailed description is needed. Traditionally, this type of learning test is used in the fear conditioning research as a verbal measure of the extent to which participants expect the unconditioned stimulus upon presentation of the conditioned stimulus(Boddez et al., 2012; Reiss, 1991). The acquisition of information conveyed by expectancy is attributed to associative learning process of classical conditioning(Boddez et al., 2013).

Declarative memory performance was tested using a cued recall procedure: Each trial started with a fixation cross signalizing the auditory presentation of the word. If participants were able to remember the associated picture they were instructed to press 'Y' and subsequently type a short description of the content of the picture. If they did not remember the associated pictures, they pressed 'N' and the next word was presented. Retrieval performance was tested twice: following learning (baseline) and after the retention interval (final retrieval). As retention score we calculated the percentage of final retrieval performance with retrieval performance at baseline set to 100%.

Cueing of associations during sleep. After learning, participants of the NREM sleep group slept for 3 hrs whereas the wake group had to stay awake during the same period and participants of the REM sleep group were allowed to sleep for 6 hrs. The rationale behind the different sleep durations for the NREM and REM sleep group is derived from the observation that the first night half is dominated by NREM sleep, while REM sleep is more dominant in the second night half. Cueing was initiated following online detection of stable NREM (four consecutive epochs of N2 or N3) or REM sleep (all criteria for REM scoring met and rapid eye movements visible) and terminated immediately when arousal or polysomnographic signs of sleep stage changes occurred. Sleep was continuously monitored by the experimenter. In the wake group, cueing of associations occurred during performance

of a computerized n-back task. The 3-h wake retention interval was divided into 30-min periods. During the first, third and fifth period, participants performed on the n-back task (including a total of 27 67-s blocks of 0-back, 1-back and 2-back, see task description for details). Participants were instructed to focus on the task and accuracy was monitored after each 30-min period.

During the retention interval, half of the words of the associations were repeatedly presented aurally via loudspeakers (50-dB sound pressure level). For each participant, the words were selected for cueing based on the last expectancy ratings. For each certainty category an automatic MATLAB algorithm chose randomly half of the words, resulting in a total of 50 words. Presentation occurred every 8,000-8,200 ms in a randomized order during 80 min (see **Table 2** for sleep parameters and number of cueing).

Table 2: Sleep and cueing parameter

	NREM	**REM**	***t***	*P*
Sleep Parameters				
Total Sleep Duration (min)	194.64 ± 4.17	354.82 ± 4.63	-25.70	**< 0.001**
N1 (%)	5.19 ± 0.62	2.90 ± 0.47	3.03	**0.005**
N2 (%)	47.22 ± 2.26	47.94 ± 2.35	-0.18	0.863
N3 (%)	30.74 ± 2.30	27.91 ± 2.59	0.70	0.492
REM (%)	13.83 ± 2.30	20.31 ± 1.03	-3.67	**0.001**
WASO (%)	2.01 ± 1.33	0.33 ± 0.15	1.59	0.122
Number of cueings				
Emotional	281.63 ± 5.12	212.89 ± 6.02	5.56	**0.001**
Neutral	267.29± 4.78	216.332 ± 7.27	3.12	**< 0.01**

WASO: Wake after sleep onset. Data are means ± SEM

n-back task

Subjects of the wake group performed on 0-, 1- and 2-back versions of n-back working memory task (Gevins & Smith, 2000). In this task, subjects are presented with a continuous stream of letters and are instructed to press a key whenever the letter 'x' occurs (0-back), or when they detect a repetition at a specified delay. In the 1-back version, subjects have to respond to immediate letter repetition (t-h-v-v) and in the 2-back version to a letter repetition with one intervening letter (t-h-v-h).

Sleep EEG

Sleep was monitored and recorded via a standard polysomnography electrode montage including EEG, EOG, submental EMG and ECG (AASM). High-density EEG (128 channel Geodesic Sensor Net, Geodesics, Eugene, OR, USA) was used to reliably estimate the topographical distributions of neuronal effects related to the cueing. Impedances were kept below 50 kΩ, while signals were sampled online at 500 Hz and referenced to the vertex electrode (Cz). In addition to the online identification of sleep stages, polysomnographic recordings were scored offline by two independent raters according to standard criteria(Iber, Ancoli-Israel, Chesson, & Quan, 2007) and discrepant scorings were solved with the aid of a third rater. In case the word presentation during REM sleep elicited an isolated K-complex but all criteria for REM scoring were met in the current, the previous and subsequent previous and rapid eye movements were visible in the same epoch, the scoring of REM sleep was continued.

Oscillatory analysis

EEG signals were preprocessed using Brain Vision Analyzer 2.0 (Brain Products, Gilching, Germany). Initially, raw EEG data were re-referenced to the average of the two mastoids and as well low-pass (100 Hz, roll-off 12 dB per octave) and high-pass filtered (0.4 Hz, roll-off 12 dB per octave). Before categorization into emotional and neutral trials, sleep EEG data were epoched into segments ranging from 1,000 ms before to 2,500 ms after word onset and trials with artifacts, e.g. due to

movements, were removed after visual inspection. REM segments were additionally corrected for eye movements using the Gratton and Coles algorithm (Gratton, Coles, & Donchin, 1983). Subsequently, segments were categorized in emotional and neutral later remembered and later forgotten associations, respectively. Three subjects from the REM and one subject from the NREM sleep group had to be excluded from the oscillatory analysis due to technical problems during data acquisition.

All succeeding EEG oscillatory analyses steps were performed using the open source Fieldtrip toolbox(Oostenveld, Fries, Maris, & Schoffelen, 2011) (http://www.fieldtriptoolbox.org) running on Matlab R2012b (MathWorks, Natick, MA). First, the data segments were averaged (evoked response) and then subtracted from the time-domain EEG signal on each trial. This was accomplished separately for each condition, electrode, and subject. The evoked (non-phase-locked) response was subtracted to isolate induced oscillations, which are thought to be generated by high-order processes (Guderian & Düzel, 2005; Singer & Gray, 1995).

Time-frequency analysis was computed for each trial by using a 7-cycle Morlet wavelet decomposition, ranging from 2 to 30 Hz in 0.5 Hz steps. A sliding window with a step size of 50 ms was applied across the entire length of the epochs. Subsequently power estimates were decibel normalized (dB power = 10*log10(power/baseline)), using a baseline window ranging from -1.000 ms to -100 ms before stimulus onset.

Slow wave analysis

The EEG segments of later remembered emotional arousing, neutral and later not remembered trials (-2000 to 4500 ms) were band-pass filtered in the range of 0.5 – 4 Hz. Slow waves were detected by a rater blind to the categories at electrode site Fz, F3 and F4 and defined as waves with a duration of more than 500 ms, exceeding an amplitude of 75 μV and initiating between 0 and 800 ms after stimulus onset.

Table 3: Slow waves after cueing

		Later remembered	Later not remembered	*t*	*P*
NREM	All	50.49 ± 2.19	44.16 ± 2.61	4.36	**< 0.001**
	Emotional	53.93 ± 2.45	44.16 ± 2.61	5.60	**< 0.001**
	Neutral	49.46 ± 2.21	44.16 ± 2.61	3.49	**0.002**
REM	All	3.43 ± 0.62	1.93 ± 0.43	2.29	**0.036**
	Emotional	4.34 ± 0.78	1.93 ± 0.43	3.42	**0.004**
	Neutral	3.11 ± 0.65	1.93 ± 0.43	1.62	0.125
		Emotional remembered	**Neutral remembered**		
NREM		53.93 ± 2.45	49.46 ± 2.21	3.13	**0.005**
REM		4.34 ± 0.78	3.11 ± 0.65	1.85	0.083

Values indicate percentage of of word presentation during NREM and REM that were followed by slow oscillations within 800 ms after word onset. Data are means ± SEM

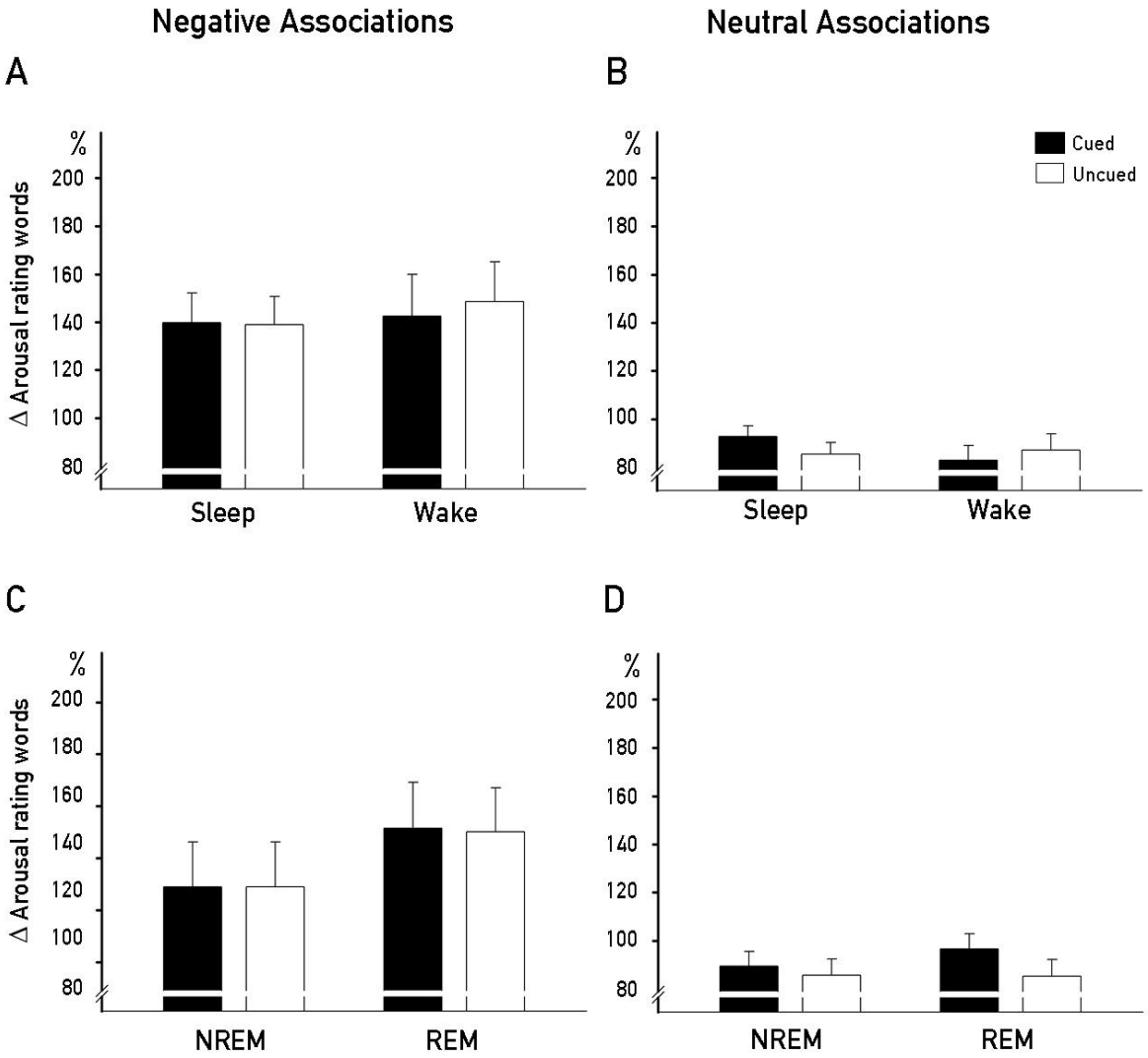
Statistical analysis

Behavioral data were analyzed using repeated analyses of variance (ANOVA) including the within-subject factor 'emotional arousal' (emotional vs. neutral) and the between-subject factors 'sleep/wake' and 'group' (NREM, REM and Wake). Post-hoc analyses were conducted using *t*-tests for pair-wise comparisons and Pearson correlations. A probability of $P = 0.05$ was set as significance threshold. For analyzing the cued recall performance we calculated separately for cued and uncued associations the changes in cued recall performance as percentage of correctly recalled associations with performance before the retention interval set to 100%. Subsequently, a *cueing benefit* score was created by calculating the difference between the memory performance of cued and uncued associations.

Statistical analyses of the EEG data was performed with a nonparametric randomization test using cluster correction(Oostenveld et al., 2011) as implemented in FieldTrip. Statistics were performed on time segments ranging from stimulus onset to 2.000 ms. The cluster alpha was set to 0.05 and 1000 randomizations were conducted for all tests. Clusters were considered significant at $P < 0.05$ (two-sided).

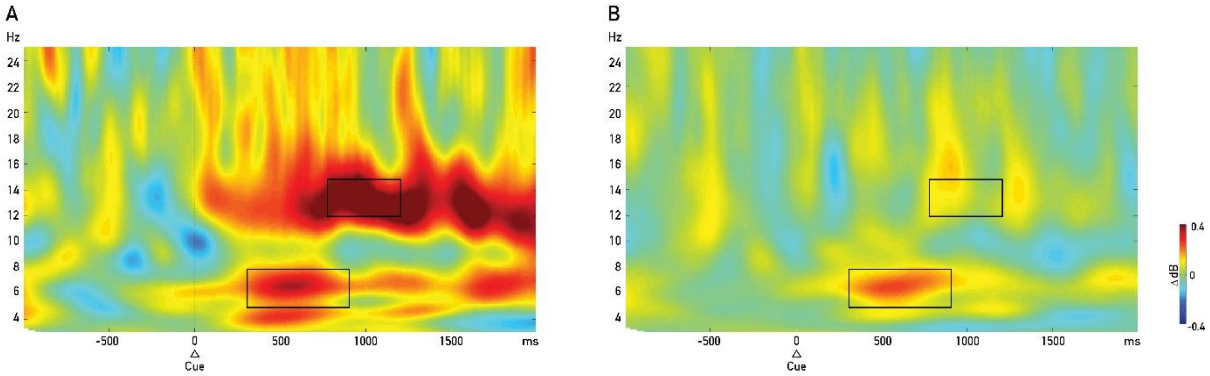
Supplementary Materials

Supplementary Figure S1: Arousal Ratings



Changes in arousal ratings of neutral words. After the retention interval, the arousal ratings for words that were associated with emotional pictures **(A + C)** during the learning phase were rated overall as more arousing as compared to words with neutral picture associations **(B + D)**. **A + B** Changes in arousal ratings after sleep did not differ from changes after a retention interval filled with wakefulness. Furthermore, arousal ratings for words associated with emotional **(A)** or neutral pictures **(B)** were not affected by cueing during sleep or wakefulness. **C + D** Changes in arousal ratings did not differ between NREM and REM group and cueing did not change arousal ratings significantly. Changes in arousal ratings are indicated as percentage of ratings giving at the end of the experimental procedure, with arousal rated before the learning phase set to 100%. Values are mean ± SEM.

Supplementary Figure S2: Oscillatory analysis



Time frequency plot for oscillatory analysis in the theta (5-8 Hz) and spindle band (12-15 Hz) for emotional and neutral trials in the NREM sleep group. Oscillatory activity after word replay (dotted line in **A and B**) was analyzed for *subsequently remembered emotional* **(A)** and *subsequently remembered neutral trials* **(B)** and contrasted with *subsequently not remembered* trials. Differences in power of theta and spindle activity were statistically tested in the time window as illustrated with the black rectangles (theta band: 300-900ms and spindle band: 800-1'200ms). Theta and spindle power were significantly higher for *subsequently remembered emotional* **(A)** and *subsequently remembered neutral trials* **(B)** as compared to *subsequently not remembered trials*.

Supplementary Table 1: Cued recall performance for categories 'Emotional' and 'Neutral'

		Cued	Uncued	*t*	*P*
NREM	Emotional				
	Learning	18.19 ± 0.81	18.24 ± 0.77	-0.77	0.942
	Retrieval	18.62 ± 0.74	17.67 ± 0.77	1.58	0.133
	Change	0.43 ± 0.51	-0.57 ± 0.33	2.11	**0.047**
	% Change	103.76 ± 3.08	97.26 ± 1.97	2.30	**0.032**
	Neutral				
	Learning	18.38 ± 0.78	18.43 ± 0.77	-0.12	0.912
	Retrieval	18.57 ± 0.78	18.43 ± 0.78	0.22	0.835
	Change	0.19 ± 0.34	0.00 ± 0.28	0.47	0.646
	% Change	101.67 ± 2.08	100.26 ± 1.63	0.61	0.553
	All				
	Learning	36.57 ± 1.46	36.67 ± 1.43	-0.14	0.891
	Retrieval	37.19 ± 1.29	36.09 ± 1.36	1.31	0.212
	Change	0.62 ± 0.63	-0.58 ± 0.38	2.13	0.046
	% Change	102.63 ± 2.15	98.71 ± 1.19	2.33	**0.030**
REM	Emotional				
	Learning	17.00 ± 0.75	17.55 ± 0.70	-1.05	0.313
	Retrieval	17.55 ± 0.94	17.50 ± 0.65	0.08	0.942
	Change	0.55 ±0.47	-0.05 ± 0.37	1.10	0.295
	% Change	102.84 ± 3.01	100.37 ± 2.16	0.79	0.449
	Neutral				
	Learning	16.40 ± 0.88	16.80 ± 0.92	-0.64	0.531
	Retrieval	16.35 ± 0.96	17.05 ± 0.92	-1.51	0.154
	Change	-0.05 ± 0.34	0.25 ± 0.26	-0.66	0.515
	% Change	99.34 ± 2.49	101.79 ± 1.69	-0.75	0.465
	All				
	Learning	33.40 ± 1.52	34.35 ± 1.50	-1.02	0.325
	Retrieval	33.90 ± 1.77	34.55 ± 1.45	-0.82	0.427
	Change	0.50 ± 0.60	0.20 0.47	0.42	0.686
	% Change	101.05 ± 2.10	101.00 ± 1.54	0.02	0.982
Wake	Emotional				
	Learning	18.10 ± 0.90	18.95 ±0.70	-1.44	0.173
	Retrieval	17.48 ± 0.98	19.14 ± 0.85	-2.97	0.014
	Change	-0.62 ± 0.45	0.19 ± 0.44	-1.80	0.092
	% Change	96.59 ± 2.73	100.90 ± 2.27	-1.85	0.084
	Neutral				
	Learning	19.00 ± 0.60	17.57 ± 0.78	2.32	**0.033**
	Retrieval	18.48 ± 0.65	16.76 ± 0.85	2.89	**0.014**
	Change	-0.52 ± 0.46	-0.81 ± 0.41	0.56	0.583
	% Change	97.63 ± 2.47	95.28 ± 2.44	0.82	0.424
	All				
	Learning	37.10 ± 1.38	36.52 ± 1.32	0.60	0.558
	Retrieval	35.95 ± 1.47	35.90 ± 1.57	0.06	0.964
	Change	-1.14 ± 0.81	-0.62 ± 0.59	-0.70	0.493

Numbers indicate either absolute values for correctly recalled pictures after presentation of the word (*Learning* and *Retrieval*), absolute change of correctly recalled associations (*Change*) or change in percentage (*% Change*) and refers to the relative difference from prior to after the retention interval, while the first recall is set to 100%. Therefore a value < 100 % indicates a decrease and a value > 100 % an increase across the retention interval. Differences between cued and uncued associations were tested statistically using paired t-test. Significant differences are marked as bold. Data are means ± SEM

Supplementary Table 2: Arousal ratings for categories 'Emotional' and 'Neutral'

		Cued	Uncued	*t*	*P*
NREM	*Emotional*				
	Baseline	2.49 ± 0.21	2.53 ± 0.21	-0.49	0.629
	Post retention	3.12 ± 0.28	3.18 ± 0.29	-0.87	0.394
	Change	0.63 ± 0.17	0.64 ± 0.21	0.09	0.929
	% Change	128.82 ± 8.70	128.34 ± 9.01	0.05	0.958
	Neutral				
	Baseline	2.37 ± 0.20	2.39 ± 0.19	-0.15	0.882
	Post retention	2.03 ± 0.18	1.94 ± 0.16	0.98	0.337
	Change	-0.34 ± 0.15	-0.44 ± 0.16	-0.87	0.394
	% Change	89.47 ± 6.48	85.82 ± 7.20	0.92	0.367
	All				
	Baseline	2.43 ± 0.20	2.46 ± 0.19	-0.46	0.649
	Post retention	2.57 ± 0.19	2.56 ± 0.18	0.36	0.720
	Change	0.14 ± 0.10	0.10 ± 0.19	0.49	0.629
	% Change	109.71 ± 6.20	105.88 ± 3.83	0.81	0.426
REM	*Emotional*				
	Baseline	2.75 ± 0.23	2.63 ± 0.24	-0.77	0.452
	Post retention	3.65 ± 0.33	2.44 ± 0.26	0.75	0.461
	Change	0.89 ± 0.31	0.76 ± 0.32	-1.12	0.278
	% Change	151.35 ± 22.83	150.05 ± 23.89	0.28	0.781
	Neutral				
	Baseline	2.62 ± 0.26	2.69 ± 0.25	-0.65	0.562
	Post retention	2.44 ± 0.26	2.24 ± 0.24	1.54	0.141
	Change	-0.18 ± 0.32	-0.45 ± 0.15	-1.56	0.136
	% Change	96.55 ± 6.75	85.38 ± 4.86	1.85	0.080
	All				
	Baseline	2.70 ± 0.23	2.75 ± 0.24	-0.88	0.391
	Post retention	3.05 ± 0.23	2.91 ± 0.23	1.61	0.125
	Change	0.35 ± 0.17	0.15 ± 0.18	1.69	0.108
	% Change	124.58 ± 14.07	116.42 ± 12.76	1.85	0.079
Wake	*Emotional*				
	Baseline	2.52 ± 0.20	2.35 ± 0.17	1.15	0.262
	Post retention	3.30 ± 0.33	3.40 ± 0.33	-1.06	0.302
	Change	0.78 ± 0.31	1.05 ± 0.28	1.71	0.103
	% Change	142.50 ± 17.32	148.55 ± 16.50	0.55	0.589
	Neutral				
	Baseline	2.33 ± 0.24	2.50 ± 0.24	-1.48	0.155
	Post retention	1.85 ± 0.24	2.08 ± 0.20	-2.73	**0.013**
	Change	-0.48 ± 0.15	-0.42 ± 0.17	0.41	0.690
	% Change	82.89 ± 6.15	87.33 ± 6.67	-0.68	0.502
	All				
	Baseline	2.42 ± 0.21	2.43 ± 0.19	-0.05	0.961
	Post retention	2.57 ± 0.20	2.74 ± 0.23	-2.29	0.033
	Change	0.15 ± 0.14	0.31 ± 0.16	-1.60	0.126
	% Change	111.06 ± 8.69	115.28 ± 7.97	-0.95	0.355

Numbers indicate absolute arousal ratings for emotional or neutral pictures after presentation of the word (*Learning* and *Retrieval*), either before the association learning task (baseline) or after learning and the retention interval. Differences between the two ratings are indicated as absolute change (*Change*) or change in percentage *(% Change*), referring to the relative difference from baseline to after the retention interval, while the first rating is set to 100%. Therefore, a value < 100 % indicates a decrease and a value > 100 % an increase across the retention interval. Differences between cued and uncued associations were tested statistically using paired t-test. Significant differences are marked as bold. Data are means ± SEM

Supplementary Table 3: Expectancy ratings for categories 'Emotional' and 'Neutral'

		Cued	Uncued	*t*	*P*
NREM	*Emotional*				
	Learning	3.23 ± 0.08	3.19 ± 0.08	1.58	0.211
	Post retention	3.15 ± 0.10	3.06 ± 0.10	1.78	0.092
	Change	-0.08 ± 0.04	-0.13 ± 0.04	1.13	0.274
	% Change	97.71 ± .1.24	95.53 ± 1.39	1.15	0.266
	Neutral				
	Learning	3.34 ± 0.08	3.26 ± 0.08	1.32	0.341
	Post retention	3.23 ± 0.09	3.18 ± 0.04	1.04	0.317
	Change	-0.10 ± 0.04	-0.08 ± 0.05	-0.23	0.824
	% Change	96.84 ± 1.34	97.35 ± 1.57	-0.28	0.782
	All				
	Learning	3.28 ± 0.07	3.23 ± 0.07	1.21	0.110
	Post retention	3.20 ± 0.08	3.11 ± 0.08	2.19	**0.045**
	Change	-0.08 ± 0.03	-0.12 ± 0.04	0.67	0.51
	% Change	97.24 ± 0.87	96.45 ± 1.17	0.65	0.52
REM	*Emotional*				
	Learning	3.03 ± 0.12	2.99 ± 0.11	1.70	0.141
	Post retention	2.98 ± 0.12	2.96 ± 0.12	0.38	0.791
	Change	-0.05 ± 0.06	-0.03 ± 0.04	-0.40	0.710
	% Change	98.57 ± 2.05	98.96 ± 1.76	-0.20	0.842
	Neutral				
	Learning	3.19 ± 0.09	3.16 ± 0.10	1.25	0.223
	Post retention	3.11 ± 0.10	3.12 ± 0.11	-0.07	0.925
	Change	-0.08 ± 0.05	-0.04 ± 0.06	-0.71	0.491
	% Change	97.48 ± 1.70	98.78 ± 1.99	-0.68	0.560
	All				
	Learning	3.11 ± 0.09	3.07 ± 0.09	1.50	0.154
	Post retention	3.05 ± 0.09	3.04 ± 0.10	0.19	0.853
	Change	-0.06 ± 0.03	-0.03 ± 0.04	-0.76	0.426
	% Change	97.87 ± 1.20	98.81 ± 1.39	-0.67	0.571
Wake	*Emotional*				
	Learning	2.92 ± 0.12	2.87 ± 0.12	1.23	0.281
	Post retention	2.85 ± 0.12	2.90 ± 0.12	-0.98	0.364
	Change	-0.07 ± 0.05	0.03 ± 0.04	-2.03	0.056
	% Change	97.71 ± 1.75	101.36 ± 1.46	-2.14	0.085
	Neutral				
	Learning	3.24 ± 0.11	3.16 ± 1.10	1.08	0.352
	Post retention	3.11 ± 0.09	2.98 ± 0.11	1.57	0.133
	Change	-0.13 ± 0.06	-0.18 ± 0.06	0.56	0.548
	% Change	96.71 ± 1.75	94.58 ± 1.82	0.81	0.434
	All				
	Learning	3.08 ± 0.09	3.01 ± 0.09	1.87	0.225
	Post retention	2.98 ± 0.09	2.94 ± 0.09	0.76	0.436
	Change	-0.10 ± 0.04	-0.07 ± 0.04	-0.58	0.578
	% Change	97.06 ± 1.44	97.76 ± 1.26	-0.47	0.684

Numbers indicate absolute expectancy ratings for words either before the association learning task (*Baseline*) or after learning and the retention interval (*Post retention*). Differences between the two ratings are indicated as absolute change (*Change*) or change in percentage *(% Change*), referring to the relative difference from baseline to after the retention interval, while the first rating is set to 100%. Therefore a value < 100 % indicates a decrease and a value > 100 % an increase across the retention interval. Differences between cued and uncued associations were tested statistically using paired t-test. Significant differences are marked as bold. Data are means ± SEM

Baseline performance and arousal ratings

After learning before the retention interval, participants generally recalled significantly more emotional associations (73.33 ± 1.66 %) as compared to neutral associations (70.19 ± 1.78 %, t_{61} = 2.43, P = 0.018, η_p^2 = 0.05), indicating the well-known modulating influence of emotion during encoding on memory performance. Importantly, no baseline differences in learning performance were observed between the NREM, REM and wake groups and cued and uncued word-picture associations, and no interactions with emotional arousal occurred (all P > 0.20, see **Supplementary Table 1** for details). Thus, we can safely exclude baseline differences in our study. Interestingly, within the emotional category, emotionally high arousing(73.41 ± 1.85 %) were better remembered as compared to emotionally low arousing associations (71.34 ± 1.93 %; t_{61} = 2.21, P = 0.038, η_p^2 = 0.06). Before the emotional association task, neutral words were rated as emotionally neutral, and these arousal ratings did not differ between words later associated with either high or low arousing pictures and were either reactivated or not (P > 0.40). This was true for all three groups individually (see **Supplementary Table 2**, for descriptive values). After the whole procedure (including the associative emotional memory task, the retention interval and the delayed cued recall testing), words associated with emotional pictures were rated as more arousing as compared to words paired with low arousing pictures (139.80± 9.32 % vs. 87.14 ± 3.27%; t_{61} = 5.53, P < 0.001, η_p^2 = 0.43; with arousal rating at baseline set to 100%; see **Supplementary Table 2**). Reflecting the emotional enhancement effect on baseline cued recall performance, words associated with emotionally high arousing (155.22± 12.02 %) were perceived significantly more arousing as compared to words associated with emotionally low arousing picture (130.04± 7.93 %; t_{61} = 3.13, P = 0.003, η_p^2 = 0.05). Thus, the arousal of the pictures generalized to arousal ratings of the word alone (without picture presentation). However, changes in arousal ratings did not significantly differ between the three groups nor did we observe an interaction with cueing of associations (all P > 0.19, **Supplementary Fig. 1**, see **Supplementary Table 2** for absolute values).

Oscillatory correlates of successful memory cueing during REM sleep

One might argue that the topographic distribution of power increases associated with subsequent reactivation effects might be different during NREM and REM sleep, and that the use of the ROI obtained from NREM sleep might be not appropriate here. Thus, we analyzed the oscillatory correlates of successful memory reactivation also during REM sleep alone. Consistent with our findings reported above, we observed no significant cluster of electrodes during REM sleep that exhibited increased power in the spindle range for later remembered as compared to later forgotten cued associations. For theta power, we again observed a significant cluster of electrodes with increased power for later remembered vs. later forgotten trials ($P = 0.024$, corrected for multiple comparisons, cluster see **Fig. 3E**). The cluster contained fewer electrodes as the cluster observed during NREM sleep, which consisted in fact of a subset of electrodes of those significantly activated by cueing during NREM sleep. Similar to the results reported above, the increase in theta activity was mainly seen for later remembered neutral associations ($t_{16} = 3.74$, $P = 0.002$, $\eta_p^2 = 0.28$), whereas theta activity in emotional and later remembered cueing did not differ significantly from forgotten cueing trials ($t_{16} = 1.77$, $P = 0.094$, $\eta_p^2 = 004$). Furthermore, the two categories of remembered associations differed significantly ($t_{16} = -2.28$, $P = 0.037$, $\eta_p^2 = 0.08$).

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IV. Upper alpha power is decreased during recall after successful NREM cueing

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Abstract

Changes in oscillatory activity in the theta and alpha band during successful memory encoding and retrieval have been repeatedly reported. A recent study has shown that recognition memory can be enhanced by cueing memories during NREM sleep. However, it is still unknown whether this can be generalized to cued retrieval of emotional pictures that were previously reactivated during sleep. Here, we investigated how neural recall mechanisms during an audiovisual association task are altered after memory reactivations during NREM sleep, by directly contrasting retrieval testing prior and after sleep. Cueing resulted in a robust preferential strengthening of negative arousing as compared to neutral memories. Generally, cueing was associated with decreases in the lower and upper alpha range during retrieval. In accordance with the behavioral result pattern, the latter was more pronounced for successfully cued and in particular for successfully cued negative associations. Our results support recent findings that cueing during sleep enhances subsequent recall-related oscillatory activity. Our findings suggest that cueing during sleep might benefit both later general attentional processing (lower alpha desynchronization) as well as facilitated access of semantic content (upper alpha desynchronization) by preferentially strengthening emotional memory traces during sleep.

Introduction

Neural oscillatory synchrony is required for memory formation (Buzsáki, 2010; Fell & Axmacher, 2011). Particularly high synchronous activity in the theta and gamma range has been consistently shown to benefit encoding and formation of declarative memory during wakefulness (Düzel, Penny, & Burgess, 2010), and it is widely assumed that theta and gamma oscillations are functionally related in binding of information involving the hippocampal system(Rey, Fried, & Quian Quiroga, 2014; Rutishauser, Ross, Mamelak, & Schuman, 2010)·(Staudigl & Hanslmayr, 2013) Interestingly, encoding and recall appear to profit also from low synchrony of oscillations in the alpha range (8 - 12 Hz) (Hanslmayr, Staresina, & Bowman, 2016; Schneidman et al., 2011; Waldhauser, Johansson, & Hanslmayr, 2012). This low-frequency desynchronization has been related to the build-up of an semantic representation in neocortical areas(Hanslmayr, Staudigl, & Fellner, 2012). The opposing pattern of synchrony has been similarly observed during retrieval testing, with increases in theta (W. Klimesch et al., 2001) and decreases in alpha power (Hanslmayr et al., 2016) associated with better memory retrieval.

Oscillatory synchrony also plays a critical role for memory consolidation during off-line periods like sleep. According the active system consolidation hypothesis, slow-oscillations (< 1 Hz) characterizing slow-wave sleep (SWS) synchronize sleep-specific spindle activity (11 – 16 Hz) with hippocampal sharp wave ripple activity to optimize the gradual redistribution of memory traces to neocortical long-term stores (Diekelmann & Born, 2010). It is assumed, that recently acquired memory traces are repeatedly and spontaneously reactivated in close association with hippocampal sharp-wave ripples, while spindle activity might ensure stabilization processes on the cortical level. According to the theory, this processes should lead to a better system consolidation of memories overnight, resulting in a stabilization of the memory trace and a better integration into pre-existing knowledge networks. Furthermore, memories with high future relevance like emotional or rewarded memories should profit the most from sleep-dependent memory formation (Fischer & Born, 2009; Payne, Chambers, & Kensinger, 2012; Wilhelm et al., 2011).

The functional role of memory reactivations for sleep-dependent consolidation processes have received strong support by experimental findings using the method of targeted memory reactivation: Re-exposure to memory cues during sleep can reactivate memories and results in improved retrieval the next day (Cairney, Durrant, Hulleman, & Lewis, 2014; Rasch, Büchel, Gais, & Born, 2007; Rudoy, Voss, Westerberg, & Paller, 2009). Remarkably, successful reactivation of memories during sleep is also strongly associated with increases in theta oscillations (Schreiner, Lehmann, & Rasch, 2015; Schreiner & Rasch, 2014), similar to oscillatory correlates of subsequent memory effects during wakefulness (Düzel et al., 2010; Fell & Axmacher, 2011). In addition, an increase in sleep-specific spindle activity has been also consistently observed. Furthermore, we have recently reported that successful reactivation of emotional memories during sleep is similarly associated with an increase in theta and spindle activity during NREM sleep (Lehmann et al., 2016, in revision). In support of the notion of a preferential consolidation of memories with future relevance during sleep, these increases were much stronger and more robust for emotional as compared to neutral memories. However, the consequences of target reactivation of emotional memories during sleep on oscillatory correlates after sleep during later retrieval testing are still unknown.

For later retrieval of neutral words after sleep, we have recently reported the targeted memory reactivation during sleep indeed results in subsequent increases in theta oscillation during successful recognition (Schreiner, Göldi, & Rasch, 2015). The increases theta oscillations over centroparietal brain regions could serve as an indicator of a stabilized and integrated memory trace by induced reactivations during sleep. Here we now examined whether this finding can be generalized to cued retrieval of emotional pictures that were previously reactivated during sleep. During the retrieval task, participants recalled the emotionality of the picture that was previously associated with the word. To control that the cueing effects are NREM specific, we presented word cues also during REM sleep and wakefulness. In our study paradigm subjects underwent two recall sessions, one prior and one after the retention interval. This enabled us to analyze cueing related effects on neural activity changes adjusted for general recall processes and to analyze changes in neural recall processes from pre to post sleep. We hypothesized that cueing increases theta (4-6 Hz) and decreases alpha

power during retrieval. In order to avoid obscuring frequency- specific effects, the importance of using narrow (8–10 Hz and 10–12 Hz) instead of broad alpha frequency ranges has been emphasized (Fink, Grabner, Neuper, & Neubauer, 2005; Klimesch, 1999). The former presumably reflecting general task demands such as attentional processes and the latter being more likely to reflect specific task requirements such as access of the semantic content of the memory trace (Doppelmayr, Klimesch, Hödlmoser, Sauseng, & Gruber, 2005; Klimesch, Vogt, & Doppelmayr, 1999; Klimesch, Doppelmayr, & Hanslmayr, 2006).

Results

Oscillatory correlates of successful memory retrieval

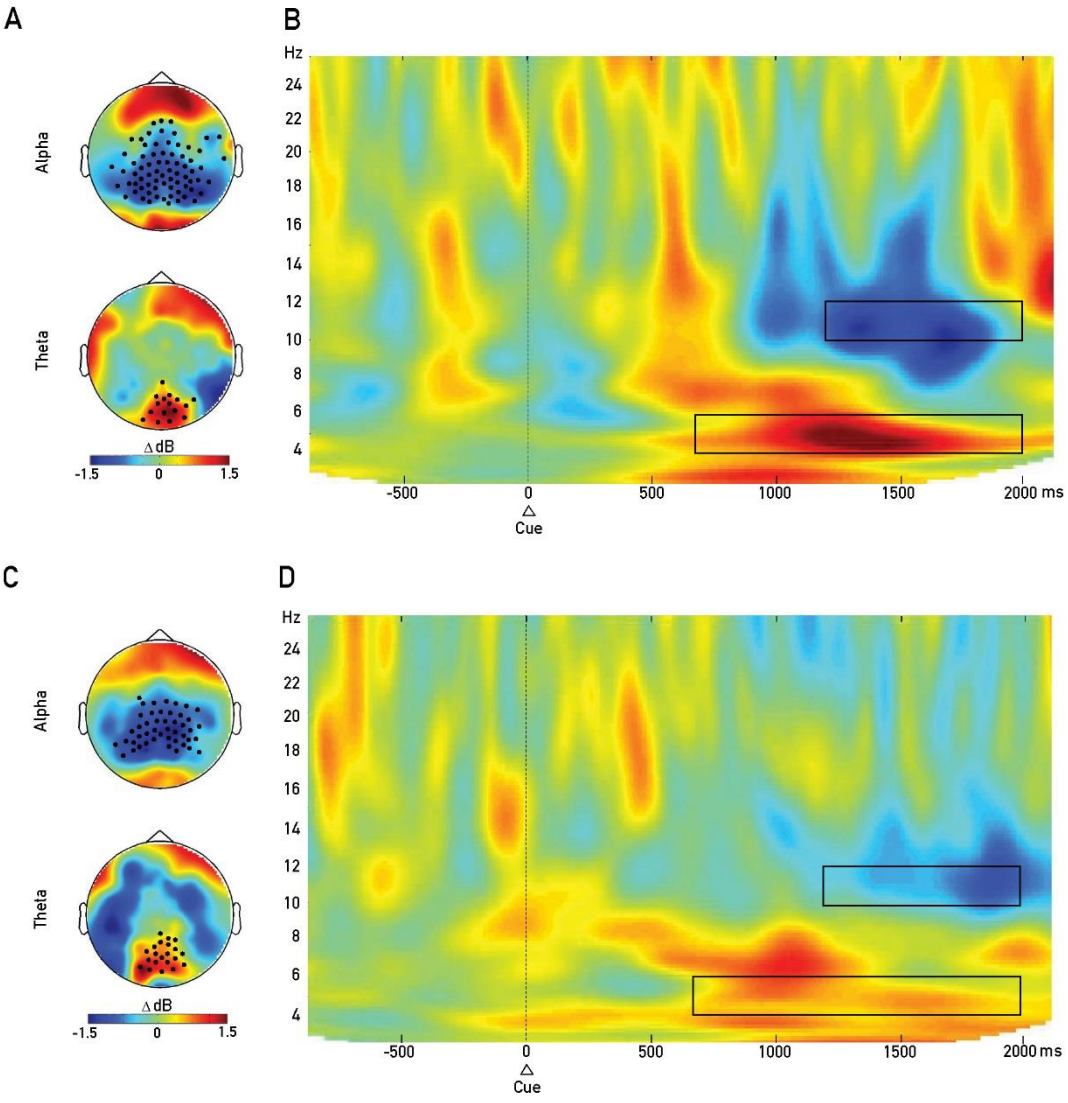
First, we analyzed the oscillatory correlates of successful memory retrieval independent of cueing during sleep in all experimental groups (i.e., classical subsequent memory analysis). In both the pre and the post retention interval measurement and in accordance with previous studies (Burgess & Gruzelier, 2000; Hanslmayr et al., 2016; Kahana, Seelig, & Madsen, 2001), we observed for all groups a significant subsequent memory effect in the theta (4-6 Hz) and upper alpha band (10-12 Hz): Theta power was significantly higher between 650ms and 2000ms in a bilateral centro-occipital cluster for remembered as compared to not remembered trials (Pre: $P = 0.01$; Post: $P = 0.02$). In a later time window (1200-2000ms), alpha activity was significantly reduced bilaterally over central electrodes (Pre: $P = 0.002$; Post: $P = 0.02$). The electrode clusters of the pre and post retention measurements are highly congruent (see **Figure 1A+B**, for power during retrieval testing before the retention interval, and **Figure 1C+D** for power during retrieval after the retention interval). Although descriptively lower, neither theta nor alpha power significantly decreased for the comparison remembered vs. not remembered from retrieval during the pre vs. the post retention interval measurement ($P = 0.45$), suggesting that overall, the oscillatory correlates of successful retrieval did not change.

Cueing effect on recall performance and oscillatory activity during retrieval

Second, we analyzed the effect of cueing during sleep on performance and oscillatory correlates during later retrieval testing. As reported previously (Lehmann et al., 2016), cueing improved recall performance only for negative associations in the NREM sleep group (significant modulation of the factor "group" by the factor "emotionality": $F_{1,42} = 4.22$, $P = 0.02$, $\eta_p^2 = 0.167$) and this benefit was significantly greater in the NREM as compared to wake group (planned post-hoc pair wise comparisons for *negative association* pairs: NREM vs. wake: $P = 0.003$, REM vs. wake: $P = 0.12$; NREM vs. REM: $P = 0.18$, see **Figure 2D**). During NREM sleep, the cueing benefit was robustly greater for negative as compared to neutral associations (NREM: $P = 0.03$; REM: $P = 0.59$; wake: P

= 0.10). In addition, cueing benefits for negative associations were significantly only in the NREM sleep group, i.e. cued negative associations were better remembered than uncued associations in this group alone ($t_{1,14}$ = 3.28, P = 0.005, η_p^2 = 0.18).

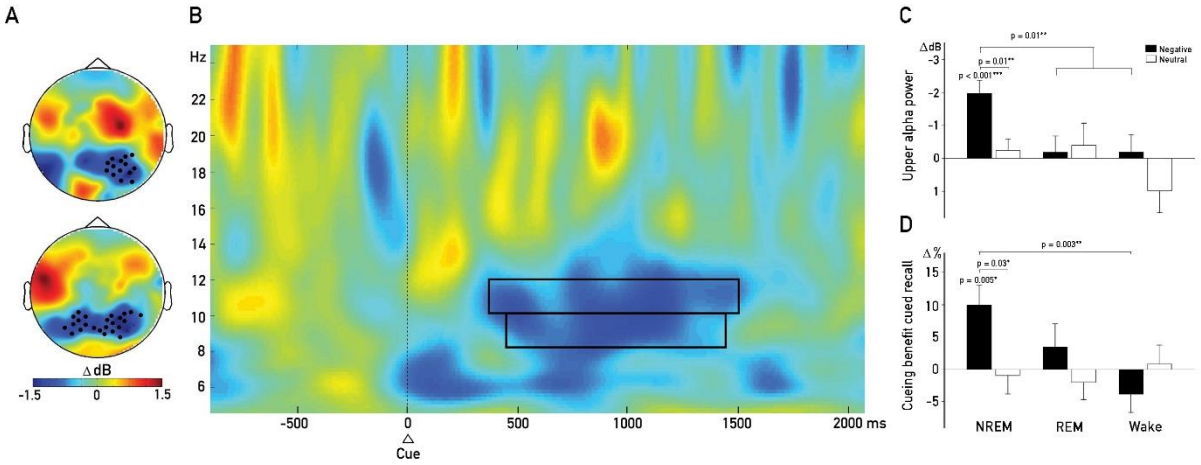
Figure 1: Memory Effect during Recall



Results for oscillatory analysis in the theta (4-6 Hz) and the upper alpha band (10-12 Hz) in all participants. Oscillatory activity after word replay (dotted line in **B and D**) was analyzed for *remembered* and *not remembered* trials in the pre (**A + B)** and post (**C + D)** measurement. **A + C** Significant cluster of electrodes in the theta (Pre: P = 0.01; Post: P = 0.02) and upper alpha band (Pre: P = 0.002; Post: P = 0.02).. Time frequency plot for the overlap of significant electrodes of the theta and upper alpha cluster in the pre (**B)** and post (**D)**. Differences in power of theta and alpha activity were statistically tested for the all 128 electrodes and time points between 100 and 2'000ms. The difference in power between *remembered* and *not remembered* (ΔdB) was significantly different in the electrode clusters as illustrated in **A + C** and in the time window as illustrated by the rectangles in **B** and **D**.

Following our main hypothesis, we analyzed the effects of cueing during sleep on the oscillatory activity during later recall testing. Accordingly, we restricted our analysis in a first step to the NREM sleep group where cueing indeed improved later recall. In order to isolate the cueing effect from general recall processes, oscillatory power of the pre-retention interval was subtracted from the post retention measurement. As predicted, retrieval of pictures that had been cued during sleep were associated with a stronger decrease in the lower and upper alpha band as compared to uncued pictures (lower alpha: $P = 0.03$ (450 – 1450ms); upper alpha: $P = 0.02$ (350 – 1500ms), see **Figure 2**) in a right centro-occipital cluster. In contrast to our hypothesis, no significant electrode cluster was observed for the comparison of cued and uncued trials ($P > 0.17$). No differences between cued and uncued pictures were observed at baseline before the retention interval in any of the three oscillatory bands (all P's > 0.17).

Figure 2: Effect of Cueing on Recall Performance and Oscillatory Activity



(**A** + **B**) Results for oscillatory analysis in the lower (8-10 Hz) and upper alpha band (10-12 Hz) after cueing during NREM sleep. Change in oscillatory activity after word onset (dotted line in **B**) from pre to post measurement was analyzed for *cued* and *uncued* trials. Differences in power of theta and alpha activity were statistically tested for all 128 electrodes and time points between 100 and 2'000ms. The difference in power between *cued* and *uncued* (ΔdB) was significantly different for the electrode clusters in the lower alpha band (**A -** lower panel) and upper alpha band (**A -** upper panel) and in the time window as illustrated by the respective rectangles in **B**. Difference in upper alpha power between *cued* and *uncued* trials (as represented by zero) was only significant for remembered negative (black bars) but not remembered neutral (white bars) associations in the NREM group (**C**), reflecting nicely the behavioral result pattern with respect to cued recall performance (**D**). Cueing of negative associations improved memory recall only when applied during NREM ($P = 0.02$), but not during REM sleep or wakefulness. Cueing of neutral associations did not affect recall performance in any experimental group (all P's > 0.55). Cueing benefits for negative associations were greater for the NREM as compared to the Wake group ($P = 0.03$) but did not reach significance when compared with the REM group ($P = 0.18$). The cueing benefit score was created by first calculating the change of correctly recalled associations for cued and uncued associations separately, with setting the performance before the retention interval to 100%. Following, the uncued was subtracted from the cued score. Values are mean SEM. *$P \leq 0.05$ **$P \leq 0.01$.

From these findings, we generated a region of interest (ROI) for the lower and a ROI for the upper alpha band, comprising only the significant electrodes. To further disentangle cueing effects on general attentional processes vs. memory processes during retrieval, we restricted the oscillatory analysis to remembered pictures only. When contrasting remembered *cued* vs. remembered uncued pictures, activity in the lower alpha ROI did not differ, however, in the upper alpha ROI, we observed a significant decrease for remembered cued as compared to remembered uncued trials (P = 0.002; 750ms-1450ms). Thus, while cueing effects on later lower alpha power might be related to more general attentional processes, cueing effects in the upper-alpha band and in the later time window might be particularly relevant for memory processes.

Subsequently, we extracted oscillatory power from the analysis on remembered pictures only within the significant time window (750ms – 1450ms) for negative and neutral associations separately. After cueing during NREM sleep, oscillatory activity in the upper alpha band nicely reflected the behavioral result pattern with respect to cued recall performance: We observed a significantly decreased activity change during the recall testing of cued remembered as compared to remembered uncued trials solely for negative and not for neutral associations (Neg: t_{14}= -4.89, $P < 0.001$, η_p^2 = 0.25; Neu: t_{14} = -0.67, P = 0.51, η_p^2 = 0.01, see **Figure 2D**). Moreover, the decrease in upper alpha activity for remembered cued vs. uncued trials was significantly stronger for negative as compared to neutral association (t_{14} = -2.88, P = 0.01, η_p^2 = 0.51, see **Figure 2).**

Independently of valence, alpha power was significantly decreased for remembered trials that were previously cued during NREM as compared to both, not remembered (t_{14} = -2.472, P = 0.03, η_p^2 = 0.15) and uncued trials (t_{14} = -5.16, $P < 0.001$, η_p^2 = 0.14; **Supplementary Figure S1)**. As a control, we applied the same analysis for the REM sleep and the wake group but they did not reveal any significant differences neither in theta nor alpha activity for the comparison remembered cued vs. uncued trials (**Figure 3**) Moreover, the extracted alpha power did not differ between cued vs. uncued negative or neutral remembered trials and between remembered and not remembered (for details for REM sleep and wake group see **Supplementary Figure S1)**.

One might speculate that the individual cueing benefit predicts the change in upper alpha power. However, using the Pearson correlation index, we found no association between the two variables (all $P's > 0.27$).

Discussion

Our results show that cueing during sleep affects oscillatory correlates of memory retrieval tested after sleep. Particularly, cueing during sleep augmented the well-known effect of alpha desynchronization during successful retrieval testing. According to Klimesch (1999), desynchronisation in the lower alpha band (8 -10 Hz) reflects allocation of attention, e.g. alertness or expectancy processes, whereas desynchronisation in the upper alpha band correlates with semantic memory performance. As reflected by the decrease in lower alpha power, cueing might generally activate attentional processes. Thus, independent of subsequent recall success, cueing during sleep facilitates allocation of processing resources in the sense that they guide search and attempts to access encoded information (Klimesch, 1997). This interpretation is highly speculative but cueing might not always stabilize memory traces but also enhance weak and labile memory traces for previously encoded associations without necessarily resulting in maintenance of the memory trace or protection from decay. When analyzing only remembered trials, we see a decrease in the upper alpha band for trials that were previously cued. Reflecting the behavioral data, the power in the upper alpha range is most decreased for cued and remembered negative associations and we observed no significant power decrease for categories that did not benefit from cueing.

Alpha power decreases during successful recognition have been repeatedly observed in both, scalp (see (Hanslmayr et al., 2012) for a review) and intracranial hippocampal EEG studies (Lega, Kahana, Jaggi, Baltuch, & Zaghloul, 2011; Staresina et al., 2016). Corroborating these findings and recent theories linking low-frequency power decreases with the coding of neural information (Hanslmayr et al., 2012; Jensen & Mazaheri, 2010; Michelmann, Bowman, & Hanslmayr, 2016) and an increase in sensory information content (Hanslmayr et al., 2016), our data suggest that the decrease in alpha power reflects the strength of a memory trace. The particular strong decrease in alpha power for remembered trials that were previously cued during NREM may reflect an increase in information (i.e. the target association) resulting from a more effective retrieval mechanism. In line

with that assumption, Staresina and colleagues (2016) observed that during retrieval, decreases in alpha power were associated with a stronger hippocampal reinstatement of the neural pattern that was recorded during encoding. Desynchronization in the alpha band (as expressed in power decreases) might support the neural representation of memories. The finding that alpha decreases were more pronounced during remembering associations as compared to items provides further support in favor of this interpretation (Staresina et al., 2016). Thus, our result of an augmented alpha desynchronization by cueing during sleep supports the notion that cueing during sleep indeed strengthens and stabilizes memory traces, thereby facilitating subsequent retrieval processes during wakefulness.

The effect of cueing on alpha desynchronization was particularly strong for emotional pictures. This is in accordance with our behavioral findings and with previous reports that the arousal evoked by the learning material during encoding critically modulates memory consolidation (McGaugh, 2004). This enhancement has been reported to increase over time, suggesting a continuing influence of emotions on consolidation processes (Kensinger, 2009), in particular if the retention interval between learning and retrieval is filled with sleep (Payne et al., 2012). Therefore the stronger decrease in upper alpha power during the recall of negative associations might be an indicator for a facilitated retrieval mechanism or an enriched informational content of the memory.

Our study results partly contrast with the findings reported by Schreiner and colleagues (Schreiner, Göldi, & Rasch, 2015). They reported that cueing of neutral words during sleep mainly results in increases in theta oscillations during later recognition testing. In the current study we only observed a general increase in theta power during successful retrieval of the associated pictures, but this theta increase was not further modulated by prior cueing during sleep. Noteworthy, the stimuli and the recall testing methods of the two studies differed considerably. While Schreiner and colleagues used associations between two neutral words, here we tested associated with neutral words and emotional and neutral pictures. In addition, the methods of retrieval testing varied: In the study by Schreiner & colleagues, participants were asked to categorize a word as 'old' or 'new'. In the current study, participants received a cue and had to indicate the emotionality of the associated picture, which might possibly explain why we did not observe effects of prior cueing on theta power.

Also in contrast with the current findings, Schreiner et al., did not report any effects of cueing on alpha desynchronization. Interestingly, alpha power was descriptively also decreased in the study by Schreiner and colleagues (see **Figure 1** in Schreiner, Göldi, & Rasch. (2015)), but it was not stable enough to survive correction for multiple comparisons. Alpha desynchronization has been considered to reflect processing of semantic information (Klimesch, Doppelmayr, Pachinger, & Russegger, 1997; Klimesch, Schimnke, & Schwaiger, 1994; Klimesch et al., 2006; Zion-Golumbic, Kutas, & Bentin, 2010) and not of features. The strong effect of cueing on alpha desynchronization might suggest that retrieval of the emotionality of the associated picture in our task mainly required accessing of semantic content of the stored memory trace, and that prior cueing during sleep had facilitated this access to semantic content particularly of emotional memories. However, this speculative reasoning has to be confirmed by future studies.

Using an associative memory paradigm, we provide empirical evidence that cueing during NREM sleep affects oscillatory activity during later retrieval testing during wakefulness. Cueing during sleep augmented alpha desynchronization during retrieval testing in both the lower and upper alpha bands, possibly indicating beneficial effects of cueing on more general attentional processes and more specify memory processes during retrieval. Importantly, the effects were stronger for emotional as compared to neutral memories, further supporting the notion of a preferential reactivation and consolidation of emotional memories during NREM sleep. Future studies need to investigate whether cueing results in a more effective retrieval mechanisms or forms a richer informational content and that the memory for the association is more vivid and therefore stronger. It also has to be further elaborated on what a decrease in alpha power means mechanistically during the retrieval and how it is related to dynamics in other frequency ranges.

Materials and Methods

Participants

Forty-five subjects participated in the three experimental groups (NREM sleep group: n = 15, REM sleep group: n = 15 and Wake group: n = 15, see **Table 1** for details). Participants were free of any medication at the time of the experiment and none had a history of any neurological or psychiatric disorders. All subjects reported a normal sleep-wake cycle and none had been on a night shift for at least 8 weeks before the experiment. On experimental days, subjects were instructed to get up at 7.00 h and were not allowed to take in caffeine and alcohol or to nap during daytime. At this point, we would like to advise the reader that parts of the reported results have already been published elsewhere (Lehmann et al., 2016). Due to EEG artifact during the recall sessions, the number of subjects differs slightly in this article.

The study was approved by the ethics committee of the Department of Psychology, University of Zurich, and all subjects gave written informed consent prior to participating. After completing the whole experiment, participants received 120 Swiss francs (CHF) (sleep groups) or 100 CHF (wake groups), respectively.

Table 1: Demographic data

	N	Age	m/f
NREM	15	22.8 ± 0.7	5/10
REM	15	21.9 ± 0.5	4/11
Wake	15	22.5 ± 0.6	5/10

Demographic data of the three experimental groups.

General procedure

Participants arrived at the sleep laboratory at 21.00 h and the experimental session started with the set-up for polysomnographic recordings, including the application of the electrodes for electroencephalographic (EEG; 128 channels, Electrical Geodesic, Inc.), electromyographic (EMG), and electrocardiographic (ECG) recordings. Prior to the experiment, participants of the sleep group were habituated to the experimental setting by spending an adaptation night in the sleep laboratory.

At ~ 22.00 h the learning phase started (for details see *The associative emotional memory task*) and after completing the learning task, participants of both sleep groups went to bed at 23.00 h and were allowed to sleep for 3 h (NREM group) or 6h (REM group), respectively whereas participants in the wake control groups stayed awake during 3h (see **Figure 3**, for an overview of the procedure). During the retention interval, a set of prior learned words was presented for ~80 minutes during sleep stages N2 and N3 for participants of the NREM group, during stage REM for participants of the REM sleep group and during wake for participants of the wake group, respectively (see *Reactivation of associations during sleep* for a detailed description).

Learning tasks

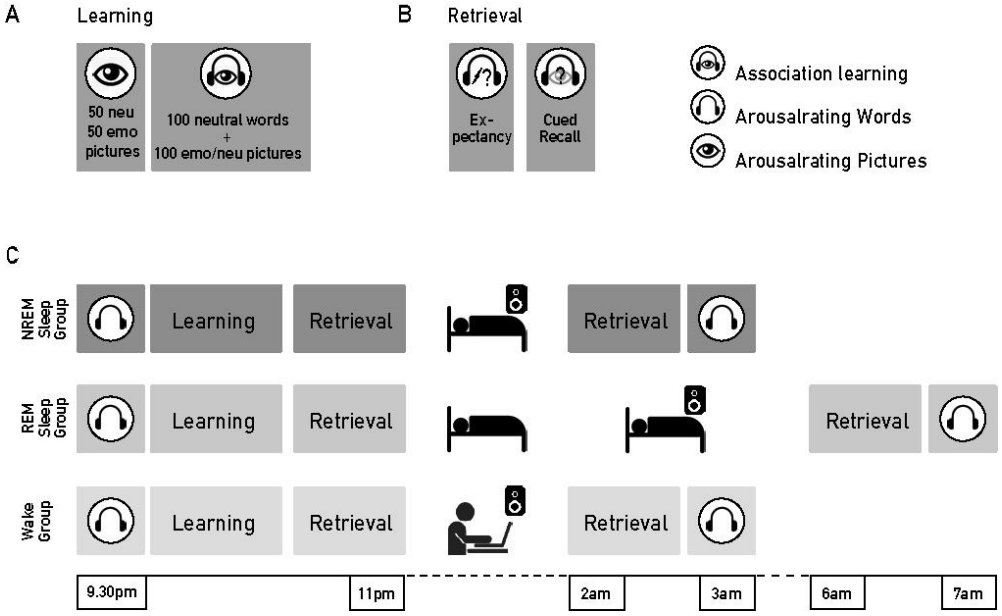
The associative emotional memory task. The associative emotional memory task consists of 100 words and pictures, which are grouped into association pairs. The words are two syllable substantives selected from the Berlin Affective Word List Reloaded (Võ et al., 2009), a German database providing normative ratings for emotional valence and arousal. The selection criterion was neutral rating with a very small standard deviation (mean rating 0 ± 0.2 SD on a -3 to +3 scale). In order to provide an auditory presentation, words were read by an actress and recorded in-house (sound file duration: 400-700ms). The set of visual stimuli consists of 100 pictures taken from the Nencki Affective Picture System (Marchewka, Zurawski, Jednoróg, & Grabowska, 2014) (NAPS). Fifty of these pictures are generally rated as neutral and low arousing. The remaining 50 pictures elicit a high level of emotional arousal and are perceived as negative in emotional valence. The associations between words and pictures were balanced across participants.

The learning phase. The associative emotional learning paradigm comprised three repetitions: During the first round, single words were presented auditory after a fixation cross (1,000 ms), followed by visual presentation of the picture on the computer screen. 1,500 ms after picture onset, the respective word was played a second time, while the picture was presented for a total duration of 2,500 ms. After a random inter-stimulus interval between 1,000-2,000 ms, the next word was presented. No response was required during the first learning round. During the subsequent two rounds, 1'500ms after the first word presentation a 7-point Likert-scale followed and participants had to indicate whether they expected a low or high arousing picture. Subjects were instructed to press '7' (or '1'), if they expected a high (or low, respectively) emotionally arousing picture, with highest certainty. The "medium" button '4' indicated no expectancy, while the remaining buttons were used for graded levels of confidence. Participants were instructed to reply fast, avoid guessing and to rely on their feelings of expectancy, rather than on explicit memory for the picture. In any case, following the key press the correct picture was presented again for 2000 ms, serving as feedback.

After a delay of 15 min, subjects underwent two types of recall testing. Using the same procedure as during the learning procedure, subjects had to indicate the expectancy of an arousing or non-arousing picture but no feedback was provided in form of the associated picture. Therefore, the response served as an index for successful implicit memory formation. In contrast to the cued recall test, expectancy ratings require only the anticipation of an event and no explicit or detailed description is needed. Traditionally, this type of learning test is used in the fear conditioning research as a verbal measure of the extent to which participants expect the unconditioned stimulus upon presentation of the conditioned stimulus(Boddez et al., 2012; Reiss, 1991). The acquisition of information conveyed by expectancy is attributed to associative learning process of classical conditioning(Boddez et al., 2013).

Declarative memory performance was tested using a cued recall procedure: Each trial started with a fixation cross signalizing the auditory presentation of the word. If participants were able to remember the associated picture they were instructed to press 'Y' and subsequently type a short description of the content of the picture. If they did not remember the associated pictures, they pressed 'N' and the next word was presented. Retrieval performance was tested twice: following learning (baseline) and after the retention interval (final retrieval). As retention score we calculated the percentage of final retrieval performance with retrieval performance at baseline set to 100%.

Figure 3: Experimental Procedure



A Before learning, all participants first rated the arousal of 100 neutral words and 50 negative and 50 neutral pictures, respectively. Then they performed on the emotionally association learning task. In this task, first a neutral word was presented via loudspeakers, followed by the presentation of an emotionally negative or neutral picture. The same word was presented a second time during the picture presentation. Participants performed on three rounds: No response was required in the first round. In the second and third round, participants rated the expectancy of a negatively arousing picture after the first presentation of the word. In any case, following the rating the correct picture was presented again serving as feedback. **B** During retrieval, participants heard the word and had to indicate the expectancy of an arousing picture (Expectancy) and provide a brief written description of the picture (Cued Recall). **C** Retrieval performance was assessed immediately after learning and after the retention interval. During the 3-h (NREM Sleep and Wake Group) or 6-h retention interval (REM Sleep Group), single word cues were presented repeatedly for 80 minutes via loudspeakers, either during NREM, REM or during performance of a computer working memory task. At the end, subjects rated the arousal level of words again.

Reactivation of associations during sleep. After learning, participants of the NREM sleep group slept for 3 hrs whereas the wake group had to stay awake during the same period and participants of the REM sleep group were allowed to sleep for 6 hrs. The rationale behind the different sleep durations for the NREM and REM sleep group is derived from the observation that the first night half is dominated by NREM sleep, while REM sleep is more dominant in the second night half. Reactivation was initiated following online detection of stable NREM (four consecutive epochs of N2 or N3) or REM sleep (all criteria for REM scoring met and rapid eye movements visible) and terminated immediately when arousal or polysomnographic signs of sleep stage changes occurred. Sleep was continuously monitored by the experimenter. In the wake group, cueing of associations occurred during performance of a computerized n-back task. The 3-h wake retention interval was divided into 30-min periods. During the first, third and fifth period, participants performed on the n-back task (including a total of 27 67-s blocks of 0-back, 1-back and 2-back, see task description for details). Participants were instructed to focus on the task and accuracy was monitored after each 30-min period.

During the retention interval, half of the words of the associations were repeatedly presented aurally via loudspeakers (50-dB sound pressure level). For each participant, the words were selected for cueing based on the last expectancy ratings. For each certainty category an automatic MATLAB algorithm chose randomly half of the words, resulting in a total of 50 words. Presentation occurred every 8,000-8,200 ms in a randomized order during 80 min (see **Table 2** for sleep parameters and number of reactivations).

n-back task

Subjects of the wake group performed on 0-, 1- and 2-back versions of n-back working memory task (Gevins & Smith, 2000). In this task, subjects are presented with a continuous stream of letters and are instructed to press a key whenever the letter 'x' occurs (0-back), or when they detect a repetition at a specified delay. In the 1-back version, subjects have to respond to immediate letter repetition (t-h-v-v) and in the 2-back version to a letter repetition with one intervening letter (t-h-v-h).

EEG recordings and analysis

We used a high-density 128-channel Geodesic Sensor Net (Electrical Geodesics (EGI), Eugene, OR, USA) to record EEG. Impedances were kept below 50 kΩ, while signals were sampled online at 500 Hz and referenced to the vertex electrode (Cz). Furthermore, EMG and ECG were recorded for standard polysomnography. In addition to the online identification of sleep stages, polysomnographic recordings were scored offline by two independent raters according to standard criteria(Iber, Ancoli-Israel, Chesson, & Quan, 2007) and discrepant scorings were solved with the aid of a third rater.

Table 2: Sleep and reactivation parameter

	NREM	**REM**	***t***	*P*
Sleep Parameters				
Total Sleep Duration (min)	183.34 ± 4.45	320.21 ± 6.55	-22.25	**< 0.001**
N1 (%)	6.13 ± 0.92	3.78 ± 0.51	2.78	**0.05**
N2 (%)	45.21 ± 2.43	44.41 ± 3.01	0.11	0.92
N3 (%)	32.32 ± 4.43	29.31 ± 2.98	0.61	0.54
REM (%)	9.23 ± 3.56	23.67 ± 1.32	-5.77	**0.001**
WASO (%)	3.90 ± 2.11	1.23 ± 0.32	1.05	0.25
Number of reactivations				
Negative	263.22 ± 11.12	231.29 ± 8.21	2.78	**0.01**
Neutral	264.24 ± 6.32	223.21 ± 8.30	4.09	**0.001**

WASO: Wake after sleep onset. Data are means ± SEM

Oscillatory analysis

Offline EEG signal preprocessing was realized using Brain Vision Analyzer 2.0 (Brain Products, Gilching, Germany). Initially, raw EEG data were re-referenced to the average of the two mastoids and as well low-pass (200 Hz, roll-off 48 dB per octave) and high-pass filtered (0.1 Hz, roll-off 48 dB per octave). The EEG data were epoched into segments ranging from 2'000 ms before to 3,000 ms after word onset. Subsequently, segments were categorized in cued/uncued and further in remembered/not remembered and negative/neutral trials, resulting in eight categories. Artifact-affected trials due to movement or meeting the following criteria were removed after visual inspection: voltage steps exceeding 100 μV/ms and voltage values exceeding 200μV. Eye blinks were removed using the Gratton and Coles algorithm (Gratton, Coles, & Donchin, 1983).

All succeeding EEG oscillatory analyses steps were performed using the open source Fieldtrip toolbox(Oostenveld, Fries, Maris, & Schoffelen, 2011) (http://www.fieldtriptoolbox.org) running on Matlab R2012b (MathWorks, Natick, MA). First, the data segments were averaged (evoked response) and then subtracted from the time-domain EEG signal on each trial. This was accomplished separately for each condition, electrode, and subject. The evoked (non-phase-locked) response was subtracted to isolate induced oscillations, which are thought to be generated by high-order processes (Guderian & Düzel, 2005; Singer & Gray, 1995).

Time-frequency analysis was computed for each trial by using a 7-cycle Morlet wavelet decomposition, ranging from 2 to 25 Hz in 0.5 Hz steps. A sliding window with a step size of 50 ms was applied across the entire length of the epochs. Subsequently power estimates were decibel normalized (dB power = 10*log10(power/baseline)), using a baseline window ranging from -700 ms to -100 ms before stimulus onset. Changes from the pre and to the post retention interval measurement were calculated by subtracting the induced power of the time frequency domain of the pre from the post measurement. Frequencies of interest included theta (4-6 Hz), lower alpha (8-10 Hz), and upper alpha (10-12 Hz). Changes in oscillatory activity were analyzed between 100ms and 2000ms after word onset.

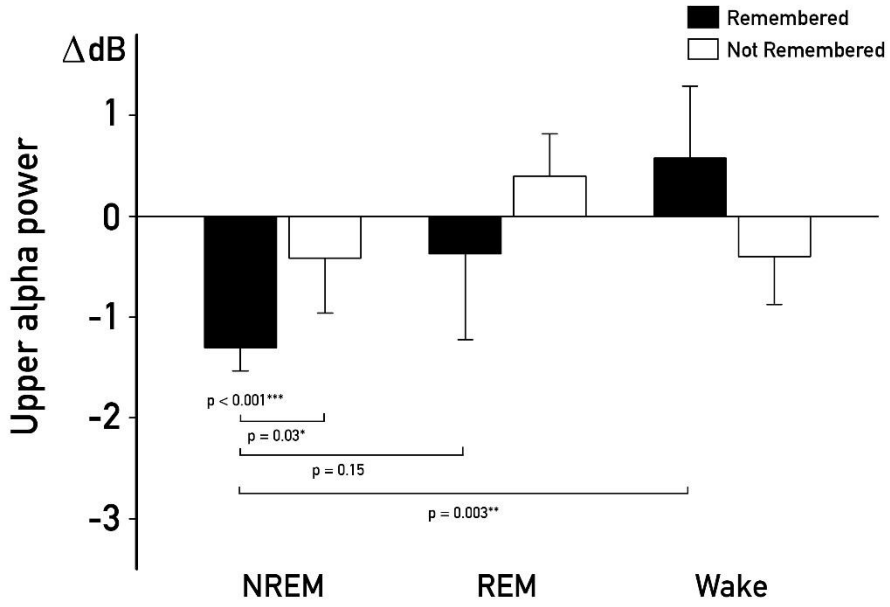
Statistical analysis

Behavioral data were analyzed using repeated analyses of variance (ANOVA) including the within-subject factors 'emotional valence' (negative vs. neutral), 'memory' and the between-subject factors 'sleep/wake' and 'group' (NREM, REM and Wake). Post-hoc analyses were conducted using *t*-tests for pair-wise comparisons and Pearson correlations. A probability of $P = 0.05$ was set as significance threshold. For analyzing the cued recall performance we calculated separately for cued and uncued associations the changes in cued recall performance as percentage of correctly recalled associations with performance before the retention interval set to 100%. Subsequently, a *cueing benefit* score was created by calculating the difference between the memory performance of cued and uncued associations.

Statistical analyses of the EEG data was performed with a nonparametric randomization test using cluster correction(Oostenveld et al., 2011) as implemented in FieldTrip. Statistics were performed on time segments ranging from 100ms to 2'000ms post stimulus onset. The cluster alpha was set to 0.05 and 1000 randomizations were conducted for all tests. Clusters were considered significant at $P < 0.025$ (two-sided)

Supplementary Materials

Supplementary Figure S1: Cueing effect on upper alpha power



Changes in oscillatory activity in the upper alpha range (10-12 Hz) after cueing.
Decreases in upper alpha power were significantly higher for remembered trials that were previously cued during NREM as compared to remembered trials that were not cued (as represented by zero). The difference (*cued* minus *uncued*) in oscillatory activity was stronger for subsequently remembered as compared to not remembered trials ($P = 0.03$). No changes in upper alpha power were observed in the REM sleep and wake group. Moreover, previously during NREM sleep cued and remembered trials showed stronger power decreases as compared to cued during REM sleep ($P = 0.15$) or wakefulness ($P = 0.003$). Values are mean SEM. $*P \leq 0.05$ $**P \leq 0.01$.

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V. Contextualization

5.1 Summary and Discussion

Emotional arousal evoked by the learning material critically modulates memory consolidation and this enhancement has been reported to increase over time, suggesting a continuing influence of emotions on consolidation processes (Kensinger, 2009), in particular if the retention interval between learning and retrieval is filled with sleep (Payne et al., 2012). According to the active system consolidation theory, memory function of sleep relies on spontaneous hippocampal memory reactivations during sleep, leading to memory reactivations in the neocortex and thereby promoting the stabilization and integration of those memories (Diekelmann & Born, 2010). While it has been suggested that the replay process during sleep is selective, preferentially strengthening memories of future relevance, e.g. associated with emotional arousal (Walker & Stickgold, 2010), the role of REM sleep in emotional memory processing remains a matter of debate. Moreover, direct evidence for the preferential replay of emotional memories during REM or NREM sleep is still lacking and the underlying neural mechanisms remain unclear, in particular whether they are different from neutral memory replay processes.

In Study 1, participants memorized associations between neutral words and emotional, either negative or positive pictures. We reported generally better memory for emotional as compared to neutral associations after learning. In contrast to previous findings, however, the recall performance for negative, positive and neutral memories did not differ after sleep. This lack of a selective emotional enhancement after sleep might be due to the task instruction, where participants were explicitly asked to learn associations and they were informed about the recall testing after sleep. Thus, neutral associations became also relevant for future behavior, and the selective consolidation of sleep for emotional memories was diminished. However, in Study 1, we verified that sleep is generally beneficial for the consolidation of the word-picture associations, as significantly more associations were recalled after sleep as compared to wakefulness. Importantly to note, no associations were replayed during the retention interval and learning and recall testing occurred in the sleep and wake group at different times of the day. Although immediate arousal ratings and recall

performance did not differ between morning and evening, possible influences of the circadian rhythm on memory consolidation cannot be excluded. Nevertheless, the task has been proven suitable for investigating mechanisms of memory consolidation during sleep and was used in Study 2 and Study 3 to induce emotional memory reactivations, in particular to test the differential effects of cueing of emotional memory during NREM and REM sleep.

In Study 2 and Study 3, the attempt has been made to describe the underlying neural mechanism during both, targeted memory reactivation and the effect of cueing on oscillatory activity during subsequent memory retrieval. On a behavioral level, we could show that (1) memory for word-picture associations can be enhanced by cueing during NREM but not REM sleep, resulting only for the former in an improved memory performance for negative arousing associations, (2) successful cueing is associated with oscillatory activity changes in the theta and spindle range and enhanced the occurrence of slow waves. During retrieval, (3) cueing effects on oscillatory alpha power, in particular for subsequently remembered trials are observable in the retrieval testing and (4) the oscillatory findings for the NREM group during cueing (Study 2) and retrieval (Study 3) nicely reflected the behavioral results, with stronger activity changes for previously cued negative remembered as compared to cued neutral remembered trials.

The stage of REM sleep has been long considered of particular importance for the consolidation of emotional memories, not least because of a marked REM sleep disinhibition in depressed patient (Pillai et al., 2011). However, direct evidence for a replay of emotional memories during REM sleep has not been reported. In Study 2 we observed no emotional enhancing effect when memories were cued during REM sleep and thus the findings in Study 2 did not indicate that memory replay during REM sleep is functionally relevant for the consolidation of emotional memories. The selection of arousing pictures comprised pictures with various contents and participants presumably perceived pictures individually different: While some might react particularly strong to real-life scenarios of open wounds and corpses, other seem to be more used to this kind of visual stimulation but are more disgusted by rotten food and unsanitary conditions. Thus, a selection of the most arousing pictures based on individual arousal ratings might counteract this confounding

effect. Interestingly, we observed a trend towards a significant cueing benefit for emotional associations when analyzing only the highly arousing half of the emotional memories. Therefore, it should be considered that during REM sleep might only highly disturbing memories are re-processed and hence consolidated. However, future studies are needed to address this issue, assessing the individual arousal elicited by the learning material. Using exclusively highly arousing stimuli would possibly strengthen the effect of cueing during REM sleep.

Memory replay during NREM sleep has been demonstrated by numerous studies. Moreover, inducing experimentally (emotional) memory reactivations during NREM sleep by cueing improves later recall, providing evidence for a functional significance of those reactivations in the process of consolidation. The NREM-specific cueing effects in Study 2 are in line with the active system consolidation hypothesis and fit well in the existing literature regarding memory reactivation. Moreover, the emotion-specificity confirms the emotional memory enhancing effect of targeted memory reactivation (TMR) during NREM sleep and is supported by a number of studies, suggesting that not only emotionality but also future relevance results in an increased chance for a memory trace to be replayed during NREM sleep (Rasch & Born, 2013). Nevertheless, the oscillatory mechanisms in humans during emotional memory reactivations remain largely unknown. Therefore, this thesis attempted to specifically describe neural activity associated with successful emotional memory reactivations during sleep. We found that cueing of subsequently remembered trials during NREM sleep was associated with increased theta and spindle power, while such cues were followed more often by surface slow waves. All three changes in oscillatory activity nicely reflected the behavioral results, with significant stronger changes for remembered emotional as compared to remembered neutral associations.

This finding is consistent with the crucial role of slow waves in models of memory consolidation during sleep. According to the active system consolidation theory, memory stabilization during NREM sleep is driven by slow oscillations synchronizing spindle-ripple events. In agreement with this notion, there is ample evidence that slow oscillations facilitate the temporally grouping of spindle and ripple activity (Maingret, Girardeau, Todorova, Goutierre, & Zugaro, 2016; Staresina et al., 2015)

and their interplay is assumed to modulate memory replay during sleep (Diekelmann & Born, 2010). More direct evidence comes from studies inducing slow oscillations experimentally or playing the tones in the up-states of the slow oscillation. The application of transcranial direct current stimulation (tDCS) at the frequency of slow oscillations (0.75 Hz) not only enhanced slow oscillations and spindle activity but resulted also in an improved memory (Marshall et al., 2006). Similarly, presenting a brief tone in the up-state enhanced the slow oscillation, associated spindle activity and the consolidation of declarative memory, indicating the crucial role of slow oscillation in memory consolidation (Ngo et al., 2013).

In Study 2, we did not synchronize the memory replay with a specific phase of the slow oscillations, therefore we cannot untangle whether the slow oscillations predicted successful cueing or were elicited by the cue presentations. Underpinning the importance of the slow waves' phase in the memory reactivation, it has been shown that memory-unrelated sounds eliciting a slow wave and further enhancing it, did not improve memory consolidation (Weigenand, Mölle, Werner, Martinetz, & Marshall, 2016). This might suggest that the natural occurrence of the slow oscillation is crucial for memory consolidation. Current attempts to detect slow oscillations continuously and to replay the memory-related cues precisely in the up-state will critically contribute to a better understanding of the role of slow oscillations in memory consolidation.

Also in line with the assumption of the active system consolidation hypothesis that sleep spindles constitute a core element of sleep-dependent consolidation mechanisms, spindle power was increased for subsequently remembered as compared to not remembered trials. Specifically, hippocampal signals of reactivation are assumed to be nested in individual troughs of spindles(Mölle, Eschenko, Gais, Sara, & Born, 2009; Siapas & Wilson, 1998) and to prime and maintain long-term potentiation in neocortical circuits (Born & Wilhelm, 2012). The observation that successful cueing was positively correlated with increases in spindle power further supports their pivotal role in memory stabilization.

Replicating a previous finding that memory cueing resulting in memory gains (trials that were not remembered before but correctly recalled after cueing) induced stronger power not only in the

spindle but also theta range (Schreiner, Lehmann, & Rasch, 2015; Schreiner & Rasch, 2014), we found also increased theta power after cue presentations of subsequently remembered associations. Unlike spindle power, the involvement of theta activity during NREM sleep in memory consolidation has only recently been implemented in a model on sleep-dependent memory consolidation (Schreiner & Rasch, 2016). During wakefulness, theta activity is consistently associated with memory formation and function in a number of species and predicts success of later recall (Klimesch, 1999; Mizuseki, Sirota, Pastalkova, & Buzsàki, 2009). Furthermore verbal cueing during sleep leads to enhanced theta activity during later recognition testing, possibly reflecting the strength of the memory trace (Schreiner, Göldi, & Rasch, 2015). It is assumed that theta activity is crucial for binding information together, particularly binding information from disparate brain regions during encoding and retrieval (Lisman & Jensen, 2013; Vertes, 2005). During NREM sleep, increased theta power is also associated with better memory consolidation in healthy participants and patients (Schabus, Hodlmoser, Pecherstorfer, & Klosch, 2005).

Interestingly, it has been demonstrated in rodents that reactivation processes seem to occur briefly before spindles emerge (Peyrache et al., 2009) and that sleep spindles are not inevitably associated with hippocampal activity (Andrade et al., 2011). Moreover, thalamic and hippocampal inputs to the cortex might even be inhibited during sleep spindles (Peyrache et al., 2011), suggesting that sleep spindles might be involved in supporting local plasticity of previously reactivated memories rather than reactivation and redistribution of memories itself (Genzel et al., 2013). In line with this assumption, not sleep spindles per se but theta activity might reflect more directly the successful reactivation and reinstatement of a memory trace, possibly with a strong association with hippocampal sharp-wave ripple activity. Thus, a successful reinstatement, as reflected by theta oscillations, accompanied or immediately followed by spindle oscillations might be required to successfully cause plastic changes that underlie stabilization and integration of memories during sleep. In support of the involvement of theta and spindle activity, it has been shown that the disruption of those oscillatory mechanisms by presenting additional auditory stimulation following reactivations might deteriorate reinstatement and stabilization processes and thereby disables the

beneficial effects of cueing during NREM sleep (Schreiner, Lehmann, & Rasch, 2015). It has however still to be resolved whether sleep spindles are actively involved in the transfer of reactivated information or rather providing a protective neural state were reactivated memories can be strengthened and stabilized undisturbed.

Although cueing during REM sleep did not improve memory performance, we observed an increase in theta activity after cueing of subsequently remembered trials. This raises the question whether memory cueing during REM sleep - similarly to NREM sleep - results in increased theta power, reflecting successful reinstatement of the related memory, but might not stabilize memory traces to the same extent due to absence of oscillatory activity in the spindle range. Surprisingly, theta power was only increased for remembered neutral and not - as one might assume - for emotional trials, which benefitted at least descriptively from cueing. Neutral associations were, however, generally less likely to be remembered previous to sleep and did not benefit from cueing. REM sleep has been traditionally implicated as being specifically involved in the processing of emotionally arousing memories (Walker, 2009). Only recently, it has been suggested that REM sleep might be critical for consolidating and enhancing the weakest rather than strong emotional memories. In a computational model on neural stability-plasticity processes (Norman, Newman, & Perotte, 2005), it has been suggested that REM sleep might be important for the strengthening of weak memories. The model states that in contrast to NREM sleep, REM sleep allows the network to rehearse the intact version of a memory even if the synaptic connections are weak. Presumably, the rehearsal mechanisms is analogous to memory replay, even if not explicitly stated by the authors. They propose a replay mechanism, guided by strong theta activity that repairs and subsequently improves the memory trace. Consistent with this model, a recent study showed that highly damaged memories by retroactive interference benefitted the most from REM sleep (McDevitt, Duggan, & Mednick, 2014). Considering the lack of a memory enhancing cueing effect, one might conclude that during REM sleep the replay mechanism for weak memories cannot be triggered externally by presenting memory associated cues. However, the increase in theta activity indicated that the word presentation elicited at least a neural response. Unfortunately, our study was not designed to address this issue

more systematically. The notion that REM sleep might strengthen only weak or memories disrupted by interference is clearly worth a closer investigation.

Another interpretation of the dissociation between behavioral and oscillatory findings for the REM sleep group is that cueing during REM sleep does not lead to a strengthening of the exact same memory trace, but leads to other memory processes involving generalization. Stickgold and colleagues (Stickgold, Scott, Rittenhouse, & Hobson, 1999) proposed that weaker associations are replayed during REM sleep, possibly playing a role in creative processes (Cai, Mednick, Harrison, Kanady, & Mednick, 2009). The stronger theta oscillatory power after cueing of neutral compared to emotional memories might also reflect a higher success of cueing rather "far-fetched" memory associations, which are less relevant for accurate remembering but possibly more involved abstraction or creativity particularly when REM sleep is experienced synergistically with NREM sleep (Walker & Stickgold, 2010).

In line with our expectations that cueing is only beneficial for memory consolidation when applied during sleep, memory reactivation during wakefulness did not improve memory recall. Descriptively, memory for negative associations was even deteriorated after cueing. This negative cueing effect for the wake group could be explained by the reconsolidation theory (see (Nader & Einarsson, 2010) for a review). After reactivations in the wake state memories revert into an active and labile state susceptible to interference, reactivation during sleep, however, immediately stabilize memories, making them resistant to interference (Diekelmann et al., 2011). The presentation of the memory cue in the wake state, i.e. the word, destabilizes the memory trace, a mechanism that is usually supporting the integration of new experiences in existing memories and play an important role during the extinction learning after fear conditioning (Hupbach, Gomez, Hardt, & Nadel, 2007; Schiller et al., 2010). Two open questions however remain and need to be addressed in future studies: First, whether the memories that were lost after cueing in the wake state are permanently lost or might be recovered or relearned with greater ease and, secondly, why only emotional memories were destabilized and not also neutral memories.

In Study 2, we did not use a sleep control group that received no cues during sleep. Hence, we cannot conclude from the results that the enhancing cueing effect exceeds the ongoing sleep-dependent memory consolidation. While it has been reported that cueing of procedural memories resulted rather in a memory bias in favor of replayed memories and at the expenses of uncued and not in an additional memory gain (Antony et al., 2012; Schönauer et al., 2014), a more recent study found that the memory performance of a no-cueing sleep group did not differ from the recall of uncued words in a cueing sleep (Schreiner & Rasch, 2014). Here, the memory performance for emotional associations in Study 1, where participants received no cues at all, and for uncued emotional associations in the NREM sleep group in Study 2 did not differ. Moreover, the general recall performance, independently of cueing and arousal, was considerably higher in the NREM sleep group and close to statistical significance. Thus, this suggests that the capacity for memory processing during a period of sleep may not be finite but that cueing even produces additional memory gains. Nevertheless, it appears that the interruption of ongoing consolidation processes by cueing during sleep might differ between categories of memory but it will need further studies addressing this issue more systematically.

The third study of this thesis investigated whether the cueing effect on memory performance is also observable in oscillatory changes during subsequent retrieval, possibly representing facilitated recall mechanisms. As pointed out above, there is abundant evidence suggesting that successful encoding and retrieval rely on neural oscillatory synchronization in theta (Fell & Axmacher, 2011) and desynchronization in alpha activity (Hanslmayr et al., 2016; Waldhauser et al., 2012). This low-frequency desynchronization during encoding has been related to the build-up of semantic representation in neocortical areas (Klimesch, 1997; Klimesch, Doppelmayr, Pachinger, & Ripper, 1997) and is assumed to reflect an increase in sensory information (Hanslmayr et al., 2012). Replicating previous findings (Burgess & Gruzelier, 2000; Hanslmayr et al., 2016; Kahana, Seelig, & Madsen, 2001), we observed that successfully recalled trials were associated with an increase in theta and a decrease in the alpha range. Cueing was associated with a general decrease in both, lower (8 -10 Hz) and upper alpha power (10 – 12 Hz). It has been proposed that desynchronisation in the lower

alpha band might reflect increased attention or expectancy processes, whereas desynchronisation in the upper alpha band is an indicator for processing of semantic memory content (Klimesch, 1999). As reflected by the decrease in lower alpha power desynchronisation in the lower alpha band (8 -10 Hz), cueing might generally enhance attentional processes during recall. Thus, independent of subsequent recall success, cueing during sleep facilitates allocation of processing resources in the sense that they guide search and attempts to access encoded information (Klimesch, 1997). This interpretation is highly speculative but cueing might not always stabilize memory traces but also enhance weak and labile memory traces for previously encoded associations without necessarily resulting in maintenance of the memory trace or protection from decay.

When analyzing only remembered trials, we observed a decrease in the upper alpha band for trials that were previously cued. Convincingly, the changes in the upper alpha power reflect the behavioral data: strongest decrease for cued and remembered negative associations and no power decrease for categories that did not benefit from cueing. Considering that both, emotionality of the learning material and cueing are assumed to result in a more effective memory consolidation, changes in upper alpha power during retrieval seem to represent a sensitive marker for memory strength. It remains, however, unclear whether cueing results indeed in a more effective retrieval mechanism. Future studies should further investigate if cueing memories during NREM sleep increases the informational content, resulting in more vivid and therefore stronger associations.

A recent study, reported stronger oscillatory theta power during successful recognition for cued as compared to uncued trials (Schreiner, Göldi & Rasch, 2015). Alpha power decrease were also evident but was not stable enough to survive correction for multiple comparisons (see **Figure 1** in (Schreiner, Göldi, & Rasch, 2015)). In contrast, we did not find cueing-related changes in theta activity, possibly resulting from the fact that we used a different type of recall. Alpha desynchronization has been considered to reflect processing of semantic information (Wolfgang Klimesch et al., 2006; Zion-Golumbic, Kutas, & Bentin, 2010) and not of features, as it is the case during the recognition for a single word. This might indicate that the stronger alpha decrease for successfully cued memories reflects an enhanced processing of semantic memory content during

retrieval of the associated emotional arousal. However, this speculative reasoning has to be confirmed by future studies.

Although dissociating from the absent behavioral changes, we reported in Study 2 cueing-related changes in oscillatory activity during REM sleep. However, in Study 3 no power changes were observed during subsequent retrieval when memory cues were presented during REM sleep. Considering the findings of Study 2 and 3 together, effects of cueing during NREM sleep were not only visible in oscillatory activity changes during cue presentation and enhanced memory performance during cued recall (Study 2) but the memory effect was paralleled by changes in alpha activity during retrieval (Study 3). Moreover, memory performance and oscillatory correlates during both, cueing during NREM sleep and subsequent retrieval were critically modulated by emotional arousal during encoding. The striking similarity of cueing-related oscillatory activity changes of neutral and emotional memories indicate that they are consolidated by similar mechanisms during NREM sleep, differing in a quantitative rather than qualitative manner. According to this "modulation hypothesis" of memory consolidation during sleep, emotion would result in a preferential replay and consolidation of memories during NREM sleep. This memory enhancing emotion effect might affect memory formation on different stages of the learning process and by various mechanisms. Two different concepts might support the understanding how emotional content is preferentially consolidated during sleep. The first assumes that the selection depends on salience tags during memory encoding and the second ascribes the enhanced integration of emotional events into preexisting affective schemata a pivotal role.

It has been proposed that motivational components affect which memories are preferentially consolidated (Diekelmann & Born, 2010). However, it is an unresolved question, whether the anticipation of a reward for optimal memory performance (Fischer & Born, 2009; Wilhelm et al., 2011) and emotional arousal during encoding modulate the same mechanisms underlying the enhanced memory consolidation. For the latter, it has been suggested that increased amygdala activation may modulate encoding of emotional stimuli in two ways: (i) filtering relevant information by altering attention and perception (Adolphs, Denburg, & Tranel, 2001) and (ii) tagging events as

important and modulating plastic processes in memory-related brain regions including the hippocampus (Bergado, Lucas, & Richter-Levin, 2011; Richter-Levin & Akirav, 2003), by releasing glucocorticoids (Wolf, 2008) and activating the epinephrinergic system (van Stegeren, 2008).

An alternative explanation for the memory enhancing effect of emotion might arises from referring to the *Component Process Model* (CPM; Scherer, 1984, 2009). During the appraisal of a stimulus, higher order cognition controls attention deployment, constantly comparing stimulus features with schemata in memory. If the appraisal results in a relevant outcome, more attention will be allocated and strongly relevant features will be stored as or related to emotional schemata in memory (Izard, 2007, 2011). According to the CPM, an emotional experience can not only activate previously established schemata with greater ease but new affective schemata are also created more rapidly. Schemata have been suggested to play a causal role in the creation of lasting associative memory representations and Tse and colleagues (2007) found that memory consolidation occurs significantly faster if a mental schema preexists into which new information can be incorporated. Recently, Lewis and Durant (2011) have described the mechanisms how the replay of memories during NREM sleep might promote the formation of and integration into existing schemata. The authors assume that memory reactivations trigger schema-related neurons that are linked to the replayed memory due to the schema activation during encoding. This results in a mutual enhancement of the newly learned memory and the schema, by which the former is strengthened and becomes gradually integrated. Taken together, the models from Lewis and Durrant and the CPM describe nicely the mechanisms how emotional information results in an increased memory and how this might be further enhanced by cueing: During encoding, affective components of the stimulus activate stronger schemata and these connections result in a positive reinforcement between the new memory and schema representations when memories are reactivated.

The present thesis aimed at investigating the enhancing effect of emotion on memory consolidation by cueing during NREM and REM sleep. Only when memory reactivation occurred during NREM sleep, emotional arousal critically modulated cueing-related memory enhancements

and the underlying oscillatory activity during reactivation and retrieval processes. Moreover, consolidation and reactivation of emotionally arousing memories during NREM sleep rely apparently on a similar mechanism as neutral memories and this mechanism is presumably modulated by the level of arousal of the to-be-consolidated stimuli already during encoding and further facilitates the triggering of targeted memory reactivations.

5.2 Future Aims

The finding that targeted memory reactivation during NREM but not REM sleep does not enhance memory for emotional associations is a crucial finding of this thesis. However, as discussed above in detail, this does not necessarily mean that REM sleep does not play a role in memory consolidation. The introduction briefly illustrated that emotion might exert its influence on two memory systems: one associated with an autonomic response and the other reflected by recall at will. While the cued recall was apparently not enhanced by cueing during REM sleep, the effect of cueing during REM sleep on the more physiological memory system has still to be investigated. Using skin conductance response and pupil dilatation as an objective measure for arousal might reveal a memory enhancing or attenuating effect during recall. Moreover, the trend towards a significant cueing effect for only highly arousing associations indicates that it might be recommended to use only trials eliciting a strong physiological response. Although emotional arousal seems to potentiate the consolidation, the question remains whether there is an optimal level of arousal for memory consolidation. It is assumed that stressful learning material may even impair consolidation (van der Kolk, 1997) and therefore the relationship between emotional arousal and memory strength is not linear.

While presenting verbal cues for emotional memories during NREM sleep improved the mere recall performance for the associated picture, it is not clear whether cueing resulted also in a more vivid memory. Cueing might stabilize the memory, reflected by recalling the same amount of pictures as the previous day. However, this provides no information about how well someone remembers the picture. Cueing during NREM sleep might increase the informational content of previously already remembered associations and thus further increases the cueing effect. Moreover, it may be that cueing during REM sleep enriches or reduces the emotional memory content. Studies assessing additionally the richness of the memory content might further contribute to untangling the differential role of NREM and REM sleep in memory consolidation.

Increasing attention for neural correlates of memory cueing during sleep has led to significant advances in the understanding of their mechanisms. Slow waves, sleep spindles, sharp-wave ripples are among the established components and theta power has been repeatedly found to be increased in association with successful cueing. Nevertheless, the precise timing and interplay between the components need still further investigations. Playing click sounds precisely in the up-state of the slow oscillation has been proven to be especially beneficial for memory consolidation, Ngo and colleagues (Ngo et al., 2013) have taken into account the neural activity before the cue presentation below 1 Hz. Analyzing the pre stimulus activity for successfully cued trials might reveal also an optimal neural state in higher frequencies ranges. It has been proposed that during encoding (in the wake state) ongoing neural processes, i.e. enhanced theta activity, occurring before stimulus are predictive for successful memory encoding (Guderian, Schott, Richardson-Klavehn, & Duzel, 2009) and retrieval (Addante & Watrous, 2011). Neural processes prior to cueing during sleep need to be described more comprehensively, possibly reflecting a particular effective neural state for memory consolidation.

This thesis did not investigate effects of emotional memory cueing in a clinical population suffering from affective disorders. Nevertheless, the emotional association learning paradigm has also been designed to address the question whether consolidation mechanisms of emotional memories differ between healthy and depressed individuals. This might be of particular significance for the following reasons: Although it is well known that depression is associated with both, an increase in REM sleep (Pillai et al., 2011) and a memory bias for negative stimuli (Ingram et al., 1998; Ridout, Astell, Reid, Glen, & Carroll, 2003), psychiatric research has only recently started to investigate sleep-related memory consolidation in clinical populations. The sensitivity towards negative stimuli has been postulated to play a critical role in the maintenance of depression. It is assumed that depressed individuals allocate more cognitive resources to the encoding negative stimuli (Watkins, Mathews, Williamson, & Fuller, 1992), show greater amygdala response during encoding (Roberson-Nay et al., 2006) and this increased activity in the right amygdala has been found to correlate in depressed more strongly with activity in the hippocampus (Hamilton & Gotlib, 2008). While depressed individuals

not only allocate more cognitive resources to negative stimuli, they also tend to ruminate more often about unpleasant experiences (e.g. (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008)). This might result on the one hand in a greater number of associations between these stimuli and preexisting material in memory and makes on the other hand memories for negative events more available shortly before going to sleep as compared to neutral experiences. The latter seems to be critical for sleep-dependent memory consolidation processes (Diekelmann & Born, 2010) and several studies suggest that a short delay before sleep onset is optimal (Gais, Lucas, & Born, 2006; Talamini, Nieuwenhuis, Takashima, & Jensen, 2008). Taken together, it remains unclear whether the negative memory bias can be merely explained by altered encoding processes or sleep-dependent consolidation of emotional memories is particularly increased in depressed patients.

To sum up, complementing the study paradigm by measurements reflecting physiological arousal during learning, retrieval and cueing during sleep and further using a higher number of pictures perceived individually as highly arousing would allow to address the question whether REM sleep plays – as suggested by our findings - indeed a negligible role in the consolidation of emotional memories or affects the memory system on another level than registered by our measurement methods. Moreover, it would be suitable to compare the results to a clinical population of depressed patients, in particular the neural mechanisms related to emotional memory reactivation.

While this thesis has answered some questions regarding the mechanisms underlying memory consolidation during sleep, many more have been raised and need to be addressed scientifically on future journeys in memory research.

VI. References

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